Diet, Nutrition, and Physical Activity in Endometrial Cancer Survivors

A thesis submitted for the degree of Doctor of Philosophy

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2017

Declaration

I, Dimitrios Koutoukidis, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Acknowledgements

I would like to express my sincere gratitude to my supervisor, Dr. Anne Lanceley, not only for the opportunity to work in this exciting area but also for trusting me to develop my ideas. Her support and guidance were critical in the project. I am also hugely grateful to my secondary supervisors, Prof Tish Knobf and Dr Rebecca Beeken, for their invaluable guidance throughout this process. Particular thanks go to my tertiary supervisor Prof Jane Wardle for her thoughtful feedback.

I would also like to thank the following individuals; this project would not be feasible without their support. Dr George Grimble for his careful direction and feedback at the early stages of the project. Sonia Lopes for sharing parts of this work, such as the intervention development, running an intervention group, and coding the qualitative data. Moscho Michalopoulou for her diligence in trial recruitment and intervention evaluation. The clinical teams at UCLH and Barts that made the recruitment process so smooth, especially Ranjit Manchanda, Philippa Lloyd, Deborah Butcher, and Nicola MacDonald. Nathalie Kliemann, Anna Roberts, and Jessica Haddrell for their help in intervention delivery. Bruce Paton, the collaborator at the Institute for Sport Exercise and Health, for his supervision in the body composition assessment. Nida Ziaudeen at the MRC Human Nutrition Research Unit at Cambridge University for the opportunity to analyse the dietary data and her attentive guidance. Dr. Lou Atkins for reviewing the intervention mapping matrices. Dr. Helen Croker for helpful discussions and guidance in the development of the intervention material. Dr. Abi Fisher and Dr. Lee Smith for providing the accelerometers for the study. Dr Matthew Burnell for statistical advice. The MSc students Alia Sukkar and Maria Papadopoulou for data entry. All members of the Trial Steering Committee for their helpful feedback. And Belinda Rahman for countless support in problem solving and for making the time in the office pleasurable.

I am extremely grateful to all participants, as this project would not be possible without their enthusiastic engagement. I would also like to thank the support groups and charities that facilitated recruitment. I gratefully acknowledge UCL for providing the generous financial support.

I would also like to thank my family who always believed in me and supported me every step of the way. Last but never least, I would like to thank my partner, Andreia, for holding my hand through the highs and lows of this journey.

Abstract

Endometrial cancer survivors comprise a high-risk group for obesity-related comorbidities. Healthy eating and physical activity can lead to better health and well-being, but this population may experience difficulties adopting healthy lifestyle practices. Personalised behaviour change programmes that are feasible, acceptable, and cost-effective are needed. Using various methodologies, this doctoral research aimed to develop and pilot a healthy eating and physical activity program. Through a systematic literature review and meta-analysis, study 1 demonstrated preliminary evidence that obesity is positively associated with overall mortality. Expanding the review, study 2 indicated that a healthy lifestyle is positively associated with health-related quality of life. Study 3 primarily piloted the instruments and procedures for the trial. Study 4, using qualitative methodology, suggested that interventions should incorporate recommendations on managing late-treatment effects, and behaviour change techniques for cognitive, practical, and social barriers to healthy lifestyle changes. Based on this feedback, an evidence-based weight management programme was adapted using the intervention mapping systematic framework in study 5. Subsequently, the programme was piloted in a phase II, individually randomized, parallel, controlled, two-site, pilot clinical trial in study 6. Adult endometrial cancer survivors (n = 60) who had been diagnosed with endometrial cancer within the previous 3 years and were not on active treatment were assigned in a 1:1 ratio through minimisation to either the 8-week, group-based, behaviour-change programme with weekly 90-min sessions about healthy eating and physical activity or usual care. Follow-up assessments were conducted at 8 and 24 weeks from the baseline assessment. The intervention, which focused on self-monitoring, goal setting, and self-incentives, was feasible in terms of recruitment, adherence, and retention. It also showed promising effectiveness. The study results will

inform the development of a randomised controlled trial to test if the programme can improve the health and quality of life of this population.

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List of abbreviations

ACS: American Cancer Society

AHEI-2010: Alternative healthy eating index 2010

ASCO: American Society of Clinical Oncology

BCT: Behaviour change technique

BCTTv1: Behaviour change technique taxonomy version 1

BMI: Body mass index

Centre TRT: Centre for Training and Research Translation

CI: Confidence interval

CRP: C-reactive protein

EBI: Evidence-based intervention

FCT: Following cancer treatment

FFQ: Food frequency questionnaire

HR: Hazard Ratio

HRQoL: Health-related quality of life

IGF-1: Insulin-like growth factor-1

IoM: Institute of Medicine

IQR: Interquartile range

LEAN: Lifestyle, exercise, and nutrition

MET: Metabolic equivalent

NCI: National Cancer Institute

NCRI: National Cancer Research Institute

NICE: National Institute for Health and Care Excellence

NIHR: National Institute for Health Research

NOO: National Obesity Observatory

PA: Physical activity

PREDIMED: Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

SCT: Social Cognitive Theory

WCRF: World Cancer Research Fund

Chapter 1 Introduction

1.1 Lifestyle and health outcomes

The observed increase in life expectancy during the last decades has been accompanied by a transition from infectious to chronic diseases, such as cardiovascular diseases and cancer, as the leading causes of death. Among others, lifestyle and behaviours have been assumed to influence disease risk. Indeed, tobacco, dietary patterns, and physical inactivity have been identified over two decades ago as the major "actual causes of death" (McGinnis and Foege, 1993).

Since then, this evidence has been replicated multiple times. The Global Burden of Diseases Study has indicated dietary factors to be the most prominent risk factor for reduced disability-adjusted life years worldwide, due to diabetes, cardiovascular diseases, and cancer (GBD Risk Factors Collaborators, 2015). This study has adopted the World Cancer Research Fund (WCRF) criteria for grading of evidence when assessing the causality between exposure and outcome and included only those pairs of exposure and outcome with convincing or probable evidence. According to the WCRF system, convincing evidence is defined as "evidence based on epidemiological studies showing

consistent associations between exposure and disease, with little or no evidence to the contrary." Probable evidence is described as "evidence based on epidemiological studies showing fairly consistent associations between exposure and disease, but for which there are perceived shortcomings in the available evidence or some evidence to the contrary, which precludes a more definite judgment." This contrasts the consideration that systematic reviews of randomised controlled trials with hard clinical endpoints, such as mortality, are the gold standard for causality inference. Indeed, observational data suffer from confounding, measurement error, and various types of bias, including selection, healthy-volunteer effect, and non-response bias. However, the use of randomised controlled trials for the examination of the relationship between each lifestyle exposure and health outcomes poses substantial ethical, methodological, and practical considerations (Satija et al., 2015). Thus, causality between lifestyle and disease has been inferred from the totality of existing evidence.

In the Global Burden of Diseases Study, obesity was the sixth and physical inactivity the 14th most prominent risk factor. When this analysis was confined to U.S. women, dietary factors, obesity, and physical inactivity were the first, fourth, and seventh, respectively, leading mortality risk factors (Marczak et al., 2016). When the dietary factors were divided into parts (e.g. diet low in fruits), high body mass index was the second major risk factor following smoking in the UK. In contrast, an overall healthy lifestyle pattern, including high dietary quality, physical activity, maintenance of a healthy weight, and non-smoking, has been associated with an average 66% lower risk of cardiovascular disease (Loef and Walach, 2012).

1.2 Diet

A dietary pattern characterised by ample amounts of whole plant foods, limited consumption of certain fats, alcohol, and processed foods high in salt, sugar, and fat, and balance of energy intake and expenditure has been consistently associated with health promotion (Katz and Meller, 2014). The health benefits of the overall dietary pattern seem to be higher than those of specific foods or food constituents (Jacobs et al., 2009). This has formed the basis of the dietary guidelines issued by governments (USDHHS/USDA, 2015, PHE, 2016) and non-profit organisations (WCRF, 2007).

A recent analysis of population data examined the dietary quality transition worldwide from 1990 to 2010 (Imamura et al., 2015). A healthy and an unhealthy dietary pattern were assessed in a scale of 0-100 with higher scores indicating healthier diets. In European and North American counties, the diet quality scores were in the range of 30-45 and 20-40 based on higher intake of healthy items and lower intake of unhealthy items, respectively, in 1990. These were among the worst scores worldwide. Two decades later, changes in the range of 0-8 points indicated modest improvements in the healthy items and deterioration in the unhealthy ones. This indicated the long-standing need for improvement in one of the prominent and modifiable risk factors for chronic disease.

1.3 Physical activity

Physical activity refers to body movements from skeletal muscle that expends energy (WHO, 2016). As with diet, physical activity is linked with health outcomes, particularly cardiovascular disease, diabetes, and cancer (GBD Risk Factors Collaborators, 2015). The global guidelines for adults recommend avoiding inactivity, at least 150 minutes of weekly moderate intensity physical activity or 75 minutes of weekly vigorous intensity physical

activity or equivalent combination, together with strength exercises at least twice a week. Doubling this amount of physical activity confers further health benefits (WHO, 2011). However, as with dietary adherence, population estimates using accelerometers suggest that about half of Europeans (46.9%) and only about 10% in the USA are meeting the minimum of aerobic physical activity guidelines with variation across counties and higher estimates for men (Marsaux et al., 2016). Once more, these estimates together with the modifiable nature of physical activity behaviour and its considerable health benefits signify a call for action.

1.4 Nutritional status and energy balance

A combination of diet and physical activity drives the energy stores of the body, which is one of the most widely studied aspects of nutritional status. A chronic higher energy intake compared to energy expenditure, namely a positive energy balance, promotes the formation of excessive adipose tissue, a state termed obesity. This positive energy imbalance is about only 50kcal/day for 90% of the population (Hill et al., 2003). Both sides of the equation (i.e. increased intake and decreased expenditure) seem to contribute to this phenomenon. The relative importance of each is yet to be determined given the extensive methodological difficulties to measure such subtle energy differences (BIS, 2012), and variation across countries exists. For example, in the USA the energy intake has increased disproportionally to the decrease in energy expenditure. UK data suggests the contrary; that the calorie intake of the population has decreased during the last decades but this has been accompanied by a larger decrease in physical activity (Millward, 2013). These phenomena are further accompanied by suboptimal dietary quality, especially in populations of lower socio-economic status, as indicated by national dietary surveys (NDNS, 2014, Wang et al., 2014). The cumulative effects are detrimental to health due to the relationship between obesity

and numerous non-communicable diseases (Kopelman, 2007) and its staggering prevalence across the world (WHO, 2012).

1.5 The effect of diet, nutrition, and physical activity on cancer

As in other non-communicable diseases, diet, nutrition, and physical activity constitute modifiable risk factors for cancer development. This link is partially explained through their contribution to obesity, which is a risk factor for eleven cancer types and contributes to unfavourable outcomes after cancer diagnosis (Ligibel et al., 2014, WCRF, 2016a). However, the mechanistic basis of this link remains unclear. Postulated mechanisms include the chronic, low-grade inflammation, higher leptin and lower adiponectin levels, and abundance of sex hormones and lipid metabolites from the dysfunctional adipose tissue in the state of obesity. Systemic changes common in obesity further contribute to cancer development. For example, hyperglycaemia induces epigenetic modifications, while hyperinsulinaemia and increased levels of insulin-growth factor 1 (IGF-1) have mitogenic effects and inhibit apoptosis (Park et al., 2014a).

On top of their effects on energy balance, both diet and physical activity have shown to independently affect the risk of various cancers, with convincing evidence of an association between processed meat and colorectal cancer, aflatoxins and liver cancer, and physical activity and breast cancer (WCRF, 2007). In measuring diet, the extensive epidemiological evidence primarily relied upon self-reported data through 24-hour recalls and food frequency questionnaires (FFQs) because of their practicality. This is because the most relevant measure of diet, individual usual dietary intake, is not directly observable. Diet is a complex system of numerous multifaceted components with day-to-day and seasonal variation (Ocke, 2013). This inherent complexity poses interpretation challenges and was the reason for the shift from reductionist approaches focused on specific nutrients or

foods towards examining dietary patterns in nutrition research (Mayne et al., 2016). Furthermore, measuring dietary intake has been notoriously challenging under free-living conditions in large populations, with both dietary instruments prone to social desirability and recall bias.

While relatively easier to capture compared to diet, assessment of physical activity has its own methodological considerations. The F.I.T.T. (frequency, intensity, time, and type) principle describes the dimensions of physical activity. Furthermore, physical activity domains include leisure, transport, occupational, and household (MRC, 2016). The ideal tool assessing all domains and dimensions of physical activity has not yet been developed. As with dietary assessment, the majority of physical activity data rely on self-report, prone to recall and social-desirability bias. Thus, the association of these exposure variables with cancer should be critically interpreted considering these limitations.

1.5.1 The effect of diet, nutrition, and physical activity on endometrial cancer

Amongst cancers, obesity seems to be most strongly linked with endometrial cancer, the most common gynaecological cancer and fourth most common cancer in women (CRUK, 2016). Each year more than 52,000, 8,000, and 99,000 cases are diagnosed in the USA, the UK, and Europe, respectively (DeSantis et al., 2014, Ferlay et al., 2013, NCIN, 2013). A meta-analysis of 26 studies involving 18,717 women demonstrated a 50% higher risk (RR: 1.50 (95% CI: 1.42-1.59) of endometrial cancer development for every 5-unit increase in body mass index (BMI) with the increase to be sharper as BMI increases (WCRF, 2013). Worldwide, about 34% of overall endometrial cancer cases seem to be attributable to high BMI; the highest percentage among cancer sites (Arnold et al., 2014). This is reflected in the staggering 72%-78% prevalence of overweight and obesity following endometrial cancer diagnosis (Crosbie et al., 2012, Arem et al., 2013b).

This estimate is significantly higher than the 58% figure observed for women in the general population (DoH, 2012) and somewhat higher than the 68% figure for women aged 65-74years (HSCIC, 2012). The aforementioned studies suggest that the BMI distribution following endometrial cancer diagnosis is shifted to the right compared to the age-matched controls (65-74y), with the prevalence of morbid obesity approximately 9% in the first compared to 2.3% in the latter. This alone may place these women at a higher risk for both morbidity and mortality compared to the general population.

Various molecular pathways have supported this observational link between obesity and endometrial cancer as reviewed by (Schmandt et al., 2011). Briefly, the excessive and dysfunctional adipose tissue secretes abundant amounts of oestrogen that promote endometrial growth. Adiposity and hyperinsulinaemia decrease serum hormone-binding globulin (SHBG) levels, further reinforcing the activity of oestrogens. The chronic inflammation contributes indirectly through the deregulation of insulin pathways. Hyperinsulinaemia, high IGF-1 levels, and low adiponectin levels activate cancer proliferating pathways in the endometrial cells. The above evidence suggests that the association is strong, consistent, plausible, with biological gradient, and, therefore, causal.

On top of the positive energy balance in the obesity state, both dietary factors and physical activity have been independently associated with endometrial cancer. Regarding diet, the glycaemic load[1] has been identified as a probable cause of endometrial cancer, based on epidemiological evidence from six cohort studies and mechanistic evidence of biological plausibility. The latter includes cancer-inducing pathways through hyperinsulinaemia and

[1] The glycaemic load of a food is calculated by the multiplication of its glycaemic index by the amount of carbohydrate in grams in its serving.

IGF-1, and oxidative stress (WCRF, 2013). In contrast, one cup of coffee probably reduces the relative risk of endometrial cancer by 7-8% irrespective of its caffeine content with biological plausibility evidence to include prevention of oxidative stress, improvements in insulin sensitivity and decreased oestradiol exposure (WCRF, 2013). Furthermore, physical activity has been negatively associated with endometrial cancer risk in cohort studies. Strong evidence of biological plausibility also exists through reduction in insulin level, improvements in insulin sensitivity, lower oestradiol levels, increased SHBG levels and indirectly through prevention of weight gain and reductions in body fat (WCRF, 2013). However, the strength of the evidence is probable for all these associations rather than convincing as with obesity.

1.5.2 Health behaviours by endometrial cancer type

It remains unclear whether health behaviours differ between the two different histological types of endometrial cancer. Type I cancers, the most prevalent ones, are adenocarcinomas, while type II endometrial cancers are clear-cell carcinomas, mucinous, and papillary serous carcinomas. While type II cancers had been thought to be oestrogen independent, and thus obesity independent, a pooled analysis of 14,069 cases indicated similar risk factors between the two types. Obesity constituted a risk factor for both types, the difference being its stronger link to type I cancers (Setiawan et al., 2013).

Further to the endometrial cancer risk, diet, nutrition, and physical activity are postulated to play a role after endometrial cancer diagnosis, a period termed cancer survivorship.

1.6 Definition of cancer survivorship

A person is considered a cancer survivor from the time of diagnosis, through the balance of their life, according to the Institute of Medicine (IoM) and the National Cancer Institute.

While this definition is the most commonly agreed, it has been highly debated (Hewitt et al., 2006). The cancer survivorship trajectory has been divided into at least three stages; the time between diagnosis and end of primary treatment, the recovery phase, and the long-term survival. Nevertheless, the term cancer survivor is practically used to describe individuals after the end of their primary treatment (ACS, 2014). The current thesis will adopt the IoM definition, but will primarily focus on examining the post-treatment period, because cancer and its treatment result in major physiologic and metabolic changes (Fearon et al., 2013) that profoundly alter the nutritional needs during treatment. Hence, different nutrition and physical activity recommendations apply for each stage of the cancer trajectory (Rock et al., 2012).

1.7 The needs of cancer survivors

Cancer survivors comprise a high-risk group for both mortality and morbidity. They can face a wide range of physical and psychosocial adverse effects, even years after the end of treatment. Physical adverse events include a high risk of cancer recurrence and an increased risk for second primary cancers, impaired physical function, pain, and fatigue. These can be coupled with obesity, and multiple comorbidities, such as cardiovascular disease and diabetes. Impaired quality of life including psychosocial factors, such as fear of cancer recurrence, depression, and social well-being further adds to the disease burden. A recent analysis of responses from 1514 cancer survivors highlighted that 38.2% report physical unmet needs, approximately 20% report financial or educational needs, and 16.4% needs related to personal control (Burg et al., 2015).

1.8 Addressing the needs of cancer survivors

The burden of disease and impaired quality of life together with the unmet needs of cancer survivors resulted in an IoM recommendation for the establishment of comprehensive survivorship plans in 2005 in USA (Hewitt et al., 2006). Along the same lines, the National Cancer Survivorship Initiative in the UK envisaged a stronger focus on recovery, health and well-being following treatment and a sustainable personalised lifestyle support for cancer survivors with them playing an active part in the decision-making (DoH, 2010). In the particular case of endometrial cancer survivors, the long-term survival and high burden of comorbidities, physical, and psychosocial issues together with the importance of healthy lifestyle behaviours for health promotion justify the need for examining their health behaviours. This is of interest given that nutrition and physical activity guidelines have been issued for cancer survivors.

1.8.1 Healthy lifestyle guidelines for cancer survivors

Nutrition and physical activity guidelines for cancer survivors have been released by the American Cancer Society (ACS) (Rock et al., 2012) and the World Cancer Research Fund (WCRF, 2007). These guidelines are summarised in Table 1.1 and are in accordance with the 2015 Dietary Guidelines for Americans (USDHHS/USDA, 2015) and the UK Eatwell Guide (PHE, 2016). They all emphasize diet quality, physical activity, and the maintenance of a healthy weight, but, interestingly, the ACS guidelines do not provide any recommendation regarding salt intake.

Furthermore, a roundtable of the American College of Sports Medicine recommended the same level of physical activity as the ACS (which is also the same for general population) based on evidence for improved physical function and HRQoL (Schmitz et al., 2010). It also noted the potential need for adaptations given the disease and treatment-related

effects. Regarding gynaecologic cancer survivors, these included seeking medical evaluation and wearing a compression garment in case of lympoedema, and additional supervision in presence of morbid obesity. No data existed on the safety of resistance exercises in the presence of lymphoedema.

The recommendations for cancer survivors relied mostly on those for cancer prevention, primarily because of the scarcity of research in cancer survivors. While generic, they follow the aforementioned evidence on health promotion. The lack of guidelines for specific cancer sites makes their interpretation and application challenging in some cases, such as in survivors of head and neck cancers that commonly suffer from malnutrition and difficulties in food intake (Rock et al., 2012). For endometrial cancer survivors, the guidelines provide a useful reference framework for the goals they should aim for, because their adherence to health behaviours is poor as discussed in the next section.

Table 1.1 Nutrition and physical activity guidelines for cancer survivors

		ACS Guidelines	WCRF Guidelines
Body weight		Achieve and maintain a healthy weight throughout life.	Be as lean as possible without becoming underweight.
Dietary pattern	Energy density	Consume a healthy diet. Limit foods and drinks with added sugar.	Avoid sugary drinks. Limit consumption of energy-dense foods (particularly processed foods high in added sugar, or low in fibre, or high in fat)
	Plant foods	Eat at least 2 to 3 cups of vegetables and 1.5 to 2 cups of fruits per day. Choose whole grains compared to refined grains.	Eat more of a variety of vegetables, fruits, whole grains, and pulses, such as beans.
	Meat	Limit processed and red meat.	Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats.
	Alcohol	Maximum two for men and one for women per day.	If consumed at all, limit alcoholic drinks to two for men and one for women a day.
	Salt	-	Limit consumption of salty foods and foods processed with salt (sodium).
Physical activity		Avoid being sedentary. Engage in at least 150 minutes per week of moderate intensity or 75 minutes per week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate and vigorous intensity aerobic physical activity. Include strength-training exercises at least 2 days per week.	Be active for at least 30 minutes every day.
Supplements		Rely on food as a source for nutrients.	Do not use supplements to protect against cancer.

1.9 Endometrial cancer survivorship

1.9.1 Health behaviours in endometrial cancer survivors

The cancer survivorship literature describes that cancer survivors often report making health behaviour changes (Demark-Wahnefried et al., 2005). A cancer diagnosis has been posited to be a teachable moment, because survivors might be more motivated to practice health-protecting behaviours. However, cancer survivors do not seem to spontaneously change their health behaviours (Williams et al., 2013b) or receive lifestyle advice from their health care professionals (Jernigan et al., 2013). In a survey of 233 endometrial cancer survivors, 70% of them reported a desire to live a healthier lifestyle more often or always after their cancer diagnosis, indicating the presence of a teachable moment that could be capitalised. 60% of them reported making dietary changes, primarily dietary fat reduction, 48% increasing their physical activity, and 62% of the overweight and obese survivors said they had attempted weight loss. They also reported initiation of weight loss with counselling from their health care providers indicating the vital position of the latter in behavioural modification (Clark et al., 2016).

However, more objective evidence of such changes is limited. The high prevalence of overweight and obesity in this population, as discussed above, is generally accompanied by low physical activity and poor dietary quality. Data from a US cohort of 152 survivors suggest only about 1% meet the current fruit and vegetable, physical activity, and non-smoking recommendations; while 57% meet only the non-smoking recommendations, and 22% meet none of the recommendations (von Gruenigen et al., 2011). Similar results have been demonstrated in a population-based US sample of 123 uterine cancer survivors, with 78% being physically inactive, 61% having less than five fruits and vegetables per day, 71% having a high fat diet (>30% fat), and 94% consuming less than the recommended 25g

fibre per day (Coups and Ostroff, 2005). In a survey of 386 Canadian survivors, only 30.6% reported meeting the 150 minutes of moderate to vigorous physical activity per week (Courneya et al., 2005) while the respective estimate in the UK is only 15% (PHE, 2015). While dietary data specifically in endometrial cancer survivors are lacking in the UK, the aforementioned data are in line with the National Diet and Nutrition Survey data demonstrating an overall low dietary quality in the UK (NDNS, 2014). The healthy-volunteer effect and the potential social desirability bias due to self-report are likely to induce an overestimation of the true population estimates of these health behaviours.

1.9.2 Health behaviours and endometrial cancer prognosis

The literature on health behaviours and endometrial cancer survival is scarce, with a handful of studies indicating no association between physical activity and mortality (Arem et al., 2013a, Arem et al., 2013b). In contrast, many studies have examined the relationship between BMI and survival, demonstrating either a negative association (Secord et al., 2016) or mixed results (Arem and Irwin, 2013). While a systematic examination of the current literature may shed more light on these associations, it is important to acknowledge the high survival rates that require considerable sample sizes and follow-up to unravel potential associations. One and five year survival rates are higher than 90% and 79%, respectively; 77% of diagnosed women are likely to survive for at least ten years (CRUK, 2016)[2]. Given the high comorbidity burden it is perhaps unsurprising that a review of 33,232 endometrial cancer cases identified cardiovascular disease as their leading cause of death. This observation was even stronger for those with early-stage and low-grade disease, who

[2] For comparison, this rate is similar to the 10-year survival in breast (78%) and prostate (84%) cancer survivors but higher than that in colorectal cancer (57%).

comprise the majority of the population (Ward et al., 2012). The cardiovascular disease outcomes further strengthen the potential utility of lifestyle behaviour change intervention in this population.

1.9.3 Health behaviours and quality of life

As with survivors of other cancer sites, endometrial cancer and its treatment negatively affect many aspects of survivors' life (Penson et al., 2006). Compared to survivors of other cancer sites, endometrial and breast cancer survivors have the highest comorbidity burden post-diagnosis (mean number of comorbidities: 2.4, SD: 0.4), according to a population-based study (Leach et al., 2015). However, another report from the same cohort found that gynaecologic (endometrial and ovarian) cancer survivors were less likely to be physically active compared to breast cancer survivors (Weaver et al., 2013). The literature suggests that adherence to lifestyle behaviour recommendations is positively associated with quality of life (Blanchard et al., 2008). However, not all studies have found the same direction or strength of the association (Lin et al., 2014). Furthermore, obesity seems to be negatively associated with quality of life in this population but the association to be attenuated by adherence to physical activity recommendations (Lin et al., 2014). As the association has not been systematically examined, one of the proposed aims of this thesis is to examine the evidence for an association between diet, nutrition, and physical activity with quality of life in this population. These associations can further inform the development of lifestyle behaviour change interventions in this population.

1.10 Summary

Taken together, the available evidence suggests that endometrial cancer survivors comprise a high-risk group for both morbidity and mortality with suboptimal lifestyle behaviours.

The evidence of an association between health behaviours and nutritional status with survival will be systematically examined in 0. As many of the long-term effects can be bi-directionally associated with diet, nutrition, and physical activity, examination of the evidence for these associations will follow in 0. Interventions to improve survivors' lifestyle behaviours tailored to their particular needs driven from cancer and its treatment may hold the potential to reduce the disease burden.

Chapter 2 Diet and physical activity behavioural interventions

The aforementioned data suggest the need for lifestyle interventions in this population tailored to their particular needs driven by the cancer and its treatment. As the cancer survivorship field is currently emerging, research on the general population and other high-risk groups might provide an initial understanding for health behaviour change in this population.

2.1 Diet and physical activity behavioural interventions for health promotion

The difficulty of changing life-term established behaviours has led to trials focusing on lifestyle behavioural counselling, pharmacotherapy, and/or interventions with specific dietary composition. Four meta-analyses of diets with various macronutrient compositions have shown inconsistent changes in weight loss and cardio-metabolic risk factors (Bueno et al., 2013, Wycherley et al., 2012, Hu et al., 2012, Ajala et al., 2013). The only consistent finding in the above meta-analyses was the strong correlation between intervention

adherence and outcomes. Large long-term interventions in diabetes management have established that the benefits of lifestyle interventions are higher than the corresponding benefits from medical interventions (Kahn et al., 2014). It has been claimed that lifestyle interventions' effectiveness should be expected to be high as long as the treatment is on-going, but is likely to decline as the intervention terminates (Pagoto and Appelhans, 2013).

There is some evidence that the mortality and morbidity risk, discussed in the introduction, could be ameliorated by lifestyle changes. However, no lifestyle trial exists to date assessing all-cause mortality as the primary endpoint. The main reason is resource constraints given the long-term follow-up and sample size in the scale of hundreds of thousands,[3] coupled with conflicts of interest and lack of potential profit for funders if industry sponsored. However, valid points can be drawn from the existing evidence. For example, the PREDIMED (Primary Prevention of Cardiovascular Disease with a Mediterranean Diet) trial in people with high risk of cardiovascular disease and the Lyon Diet Heart Study in people after a myocardial infarction indicated a 30% and 70% risk reduction for cardiovascular disease with Mediterranean dietary patterns, respectively (Estruch et al., 2013, de Lorgeril et al., 1999). In contrast, the LOOK Ahead trial observed no cardiovascular benefit comparing an intensive weight loss program (energy restriction and physical activity) with diabetes support and education in adults with type-2 diabetes and affected by overweight or obesity. Potential reasons include the low rate of cardiovascular events in both trial arms and the higher use of cardio-protective drugs in the control group despite the sustained 6% weight loss in the intervention arm at 9.6 years follow-up (vs. 3.5% in the control arm). However, benefits of the intensive lifestyle intervention included diabetes remission, clinically significant improvements in overall HRQoL, physical

[3] http://www.predimed.es/investigators-tools.html

function, pain, depression, body image satisfaction, and lower risk for chronic kidney disease, retinopathy, other comorbidities, and no serious adverse effects (Delahanty, 2014).

A meta-analysis of diet and physical activity interventions in people with impaired glucose tolerance demonstrated a 50% risk reduction of type 2 diabetes (Gillies et al., 2007). In healthy adults, another meta-analysis has shown that dietary advice effectively promoted modest changes in cardiovascular disease biomarkers, including blood pressure, and total and LDL cholesterol over a 1-year period (Rees et al., 2013). Furthermore, the interventions were effective in promoting dietary behaviour change, but the large heterogeneity observed, possibly given the self-report of dietary intake, suggests caution in the interpretation of these results. However, these behaviour changes are generally modest even for the most motivated individuals (Webb and Sheeran, 2006). Furthermore, most interventions are generally resource intensive and engage primarily participants with relatively healthy baseline lifestyles and, therefore, do not engage individuals who are most in need.

In conclusion, diet and physical activity behavioural interventions have the potential to positively affect health outcomes. Their translation to cancer survivors primarily depends on their acceptability, practicability, effectiveness, and affordability in the new setting. The next section examines the behavioural interventions that have been carried out in cancer survivors.

2.2 Diet and physical activity behavioural interventions in cancer survivorship

2.2.1 Survival outcomes

Cancer recurrence and survival are attractive primary endpoints in cancer survivorship research. The aforementioned strong epidemiological and mechanistic evidence between lifestyle and cancer incidence is coupled with longitudinal studies indicating the potential for lifestyle to positively impact cancer survivors. One of the limitations of the cancer survivorship literature is its justifiable focus on breast cancer due to its prevalence but which limits the generalisability of the findings. The other limitation is the predominance of physical activity trials, versus multiple behaviour trials or diet-specific trials. Despite the scarcity of multiple studies for other cancer sites, the WCRF continuous update project ranked the evidence on obesity, diet, and physical activity in breast cancer outcomes as limited (WCRF, 2014).

In terms of intentional weight loss, strong evidence for its benefits in cancer survival outcomes is currently lacking. The WINS study is the only study that reported a significantly lower breast cancer recurrence in survivors who were assigned to a low-fat diet and experienced moderate weight loss compared to controls (Chlebowski et al., 2006). In contrast, no significant differences were observed in any breast cancer survival outcome in the WHELS study that tested a dietary intervention high in vegetables, fruits, and dietary fibre, and low in fat (Pierce et al., 2007). However, participants did not lose weight in the WHELS study and this has been postulated to be one of the reasons for the differences in the results. An adaptation of the Look AHEAD weight loss trial with an estimated sample of 3,200 breast cancer survivors will examine the merits of intentional weight loss in breast cancer recurrence (Gallagher, 2016). Similarly, the "Colon Health and Life-Long Exercise

Change" (CHALLENGE) trial is expected to report by 2030 on the effects of a structured 3-year exercise intervention including face-to-face counselling, supervised exercise, written and telephone support, and behavioural modification on disease-free survival in colorectal cancer survivors (Courneya et al., 2016).

As with survivors of other cancer sites including breast, endometrial cancer survivors have a high comorbidity burden and are more likely to die from non-cancer causes, primarily cardiovascular disease (Arem et al., 2013b). Therefore, healthy lifestyle interventions focusing at improving HRQoL and targeting prevention and management of functional impairment and co-morbidities might be as relevant as cancer-specific outcomes to patients, physicians, and commissioners but it has been claimed that this primarily depends on their values (Goodwin, 2016). While strong evidence in endometrial cancer survivors is lacking (as systematically examined in 0), studies in survivors from other cancer sites might provide valuable context.

2.2.2 Biomarkers

Evidence from interventions in breast, colorectal, prostate and gastric cancer survivors suggests that physical activity after cancer diagnosis positively influences various prognostic biomarkers. A systematic review of eleven randomised clinical trials suggested that physical activity improved insulin, insulin-like growth factor-1 (IGF-1), and IGF-1 binding proteins and anti-inflammatory biomarkers, such as C-reactive protein (CRP), but the changes were not consistent across studies (Ballard-Barbash et al., 2012). Limitations included the diverse methodology for physical activity assessment, lack of statistical power, potential selection bias during recruitment, and small number of studies assessing each biomarker. Furthermore, dose-response effects or effects by type of exercise could not be examined. Clearly, whether biomarker changes will influence clinical endpoints in the long term

remains unclear, but, on balance, they provide a valuable surrogate that, if interpreted in the context of epidemiological and experimental evidence on physical activity, provides a substantial argument for the benefits of physical activity on overall health in this population.

Furthermore, secondary outcome analysis from the Lifestyle, Exercise, and Nutrition (LEAN) study, a behavioural weight loss intervention in breast cancer survivors, indicated significant improvements in CRP over the 6-month program compared to usual care but no improvements in other biomarkers (Harrigan et al., 2016). In sub-group analyses, CRP, interleukin-6, and leptin were improved with weight loss greater than 5%, while insulin, glucose, and TNF-α were not but the multiple tests for secondary outcomes makes them prone to type I (false positive) error. These results have not been confirmed from other similar trials. No changes in inflammatory cytokines and insulin pathway biomarkers were observed after one 12-week intervention and another 24-week intervention involving supervised exercise sessions and dietary counselling compared to control arms in breast cancer survivors (Swisher et al., 2015, Scott et al., 2013). However, both were secondary analyses of underpowered trials that does not allow for safe conclusions.

2.2.3 Body composition

Diet and physical activity also affect body composition. The latter is another surrogate outcome of interest, as excess adiposity has not only been associated with chronic diseases but also its other components, including muscle mass, influence health outcomes (Kalyani et al., 2014).

In breast cancer survivors, a review of weight loss interventions indicated that seven out of eight studies reported significant reductions in percentage body fat. Two of the four assessing lean body mass indicated small but significant reductions (Reeves et al., 2014).

Another behavioural weight loss intervention did not find significant differences in muscle mass and bone mineral density at the end of the 6-month intervention compared to control group (Harrigan et al., 2016). A 6-month healthy eating and physical activity intervention in prostate cancer survivors including 12 telephone sessions and tailored materials resulted in significant reductions in fat mass but no change in lean mass compared to control group, as subjectively estimated by skinfold thickness (O'Neill et al., 2015). Modest loss of lean mass is expected during weight loss (Hall et al., 2011) but this might not be a particular concern in cancer survivors diagnosed in middle age. However, it might be a considerable problem for older cancer survivors, as muscle mass loss can indicate lower physical function and worsen prognosis. This issue is further discussed in Chapter 3.

Six- to 12-month intensive aerobic and/or resistance exercise interventions that were both supervised and home-based preserved bone mineral density compared to bone loss under control conditions in breast cancer survivors (Dieli-Conwright and Orozco, 2015). Mechanistic evidence suggests that the movement-related mechanical loading stimulates bone mechanoreceptors that enhance osteoblastic activity. While endometrial cancer survivors may not face bone loss related to adjuvant endocrine treatment as breast cancer survivors (Knobf et al., 2016), treatment-induced menopause leads to reductions in bone-preserving oestrogen. Data on bone mineral density in endometrial cancer survivors are sparse as mentioned above, but menopause is an established risk factor for osteoporosis (Riggs et al., 1998).

2.2.4 Health-related quality of life

The effect of lifestyle behavioural interventions on overall HRQoL and its subscales in endometrial cancer survivors is systematically reviewed in 0, but the literature on cancer survivors overall formed the basis for this systematic examination. A Cochrane meta-

analysis of 40 randomised exercise trials demonstrated improvements of medium size in overall HRQoL in cancer survivors at 12 weeks and 6-month follow-up (Mishra et al., 2012). Most studies included survivors post-treatment, but had considerable variation in the mode of the intervention, used diverse HRQoL measures, and were at high risk of methodological biases rendering a cautious interpretation of their results.

The RENEW lifestyle intervention, detailed in the next section, and a small 6-month intensive behavioural weight loss program including exercise sessions and dietary counselling also demonstrated improvements in overall HRQoL (Scott et al., 2013, Morey et al., 2009). On the other hand, the "CanChange" trial, a less intensive 6-month telephone-based behavioural counselling intervention, did not show improvements in HRQoL (Hawkes et al., 2014a). However, lifestyle behavioural trials with pre-specified powered analysis on overall HRQoL are lacking in cancer survivors.

2.2.4.1 Physical well-being

Physical function and well-being are critical outcomes for cancer survivors, because most cancer survivors are older adults and are at high risk of functional decline. The "Reach out to Enhance Wellness in Older Cancer Survivors" (RENEW) study tested a one-year, home-based, lifestyle intervention aiming at realistic weight loss, improving dietary quality, and physical activity in overweight, sedentary, older cancer survivors, who were primarily white and highly educated. While the intervention did not increase baseline physical function measured through questionnaire administration, it demonstrated a significant reduction in the progression of functional decline at one-year follow-up compared to wait-list control (Morey et al., 2009). Statistically but not clinically significant changes in self-reported weight were observed in both immediate (mean loss 2.4kg) and delayed (mean loss 0.9kg) interventions at one year, but relative changes in lean and fat mass could not be

assessed. These were accompanied by small and substantial improvements in dietary quality and physical activity, respectively. These behavioural changes were maintained one year after intervention completion, with the exception of fruit and vegetable intake that decreased. However, the decline in physical function was much sharper in the year after intervention cessation (Demark-Wahnefried et al., 2012), indicating that the beneficial effects of the intervention decline with intervention completion and that more research on the maintenance of the behaviours is warranted. Secondary analysis of this intervention verified the aforementioned importance of adherence to the intervention (Winger et al., 2014). Telephone counselling adherence (which was based on Social Cognitive Theory (SCT) and the trans-theoretical model) facilitated improvements in physical function, mental health, and BMI through improvements in health behaviours. Of those health behaviours, endurance exercise showed the most promising effects. However, this might have reflected a low participation in strength exercises, which was not assessed in the study. Dietary intake of fruits and vegetables was associated with functional improvements, while saturated fat intake was not associated with any health outcome. A more holistic view of the dietary intake, as provided by diet quality indices, could have provided more insight into dietary changes.

The ENERGY ("Exercise and Nutrition Enhance Recovery and Good Health for You") behavioural weight loss trial has been the largest, longest, and statistically powered one to examine physical function and vitality in breast cancer survivors. The year-long intensive intervention aimed at weight loss, calorie restriction, and adherence to the ACS lifestyle guidelines (Table 1.1) through 52 group sessions and telephone counselling contacts and was compared to two in-person counselling sessions. The intervention resulted in clinically meaningful weight loss (6% vs. 1.5% in control) and increases in self-reported physical activity minutes at intervention completion with subsequent weight regain and physical

activity decline in the following year (Rock et al., 2015). Dietary data have not yet been reported, therefore, not allowing for examination of the behavioural effects of the intervention and participants' adherence to the guidelines. Despite the temporal effectiveness in weight loss and physical activity, the study demonstrated non-significant changes in both physical function and vitality at intervention completion and one year thereafter (Demark-Wahnefried et al., 2015).

Only the "CanChange" trial has been powered to examine the effects of behavioural counselling on physical HRQoL in colorectal cancer survivors. The six-month telephone counselling on multiple health behaviours did not change physical (or mental) HRQoL significantly at intervention completion and one-year follow-up compared to usual care (Hawkes et al., 2013). Speculated reasons included high baseline function, ceiling effects of the questionnaire, modest increase in physical activity of 11 min on average at last follow-up, and small or no changes on vegetable, fruit, and fibre intake.

2.2.4.2 Fatigue and pain

The above-mentioned Cochrane review indicated moderate quality evidence from ten trials that exercise in cancer survivors significantly improved fatigue at 12-week follow-up but only low quality evidence from three trials for significant improvements at 6-month follow-up (Mishra et al., 2012). This suggests that benefits are sustained only with continued exercise. Two recent meta-analyses of five and 14 exercise trials in colorectal and breast cancer survivors, respectively, found no significant short-term changes in fatigue (Cramer et al., 2014, Zhu et al., 2016). However, the latter meta-analysis had high heterogeneity, even when the analysis separated modes of exercise (Zhu et al., 2016). A systematic review of exercise trials in prostate cancer survivors suggested improvements in fatigue with exercise interventions. Given the aforementioned limitations of meta-analysing exercise

interventions and that most studies used standardised self-reported measures of fatigue, the mixed results might be due to differential effects among cancer survivor groups or due to the extent of exercise adherence and variation in the mode of delivery.

Fatigue did not improve in the "CanChange" trial (Hawkes et al., 2013) or the aforementioned trial on prostate cancer survivors (O'Neill et al., 2015). In contrast, fatigue improved after 12-week telephone-based behavioural counselling in a small trial in breast cancer survivors which modestly improved dietary quality but not physical activity (Kim et al., 2011). Additionally, fatigue was reduced in cancer survivors at completion of the "Kanker Nazorg Wijzer (Cancer Aftercare Guide)" intervention (Willems et al., 2016). This was a 6-month, web-based intervention addressing psychosocial issues and smoking together with healthy eating and physical activity yielding modest improvements in self-reported moderate physical activity and vegetable intake but not in other dietary outcomes (Kanera et al., 2016). Modest behavioural changes, standardised yet different outcome measures, non-response bias (e.g. the healthy volunteer effect), and underpowered analysis might account for these mixed findings.

Regarding pain, the Cochrane meta-analysis indicated short-term improvements with exercise intervention, but those were of smaller scale compared to changes in fatigue (Mishra et al., 2012). The RENEW lifestyle intervention did not demonstrate significant changes in pain (Morey et al., 2009) but no other lifestyle trials have reported on pain as a secondary outcome.

2.2.4.3 Psychological well-being

Exercise also improved emotional well-being and reduced depression and anxiety scores in breast cancer survivors based on a meta-analysis of nine, eight, and seven randomised exercise interventions, respectively (Zhu et al., 2016). No statistical heterogeneity was

observed but the pooled studies had again variable methodological rigour, duration, intensity, frequency, and mode of physical activity tested; characteristics that pose challenges in the interpretation of the results. Analogous results were demonstrated in the aforementioned Cochrane meta-analysis with improvements in emotional well-being and anxiety, and positive trends for depression (Mishra et al., 2012).

Lifestyle interventions such as the "CanChange" and the RENEW trial did not find significant differences in emotional well-being (Hawkes et al., 2014a, Morey et al., 2009). A unique finding from the ENERGY trial indicated no differences between groups at intervention completion but a significantly higher depression score in the intervention group at two-year follow-up (Demark-Wahnefried et al., 2015). Although risk false positive error was high, the weight regain observed at follow-up might be positively associated with depression, as acknowledged by the authors and observed in women in the general population (Cachelin et al., 1998). Therefore, there might be a need to strongly target these issues during lifestyle interventions.

2.2.5 Summary of interventions in cancer survivors

In conclusion, healthy eating and physical activity interventions seem to have a favourable impact on various surrogate outcomes in cancer survivors. However, the aforementioned behavioural interventions had variable delivery modes, duration, dose, and yielded differing degrees of effectiveness that makes their direct comparison and translation in other settings challenging. Given the resources required to sustain behavioural change that leads to fruitful health benefits (Delahanty, 2014), understanding the common behavioural components of lifestyle interventions and tailoring them in a cost-effective way with large-scale applicability shall be vital for future research, practice and policy.

2.3 Aims of the research

Based on the above, research on the survivorship population is of considerable importance. The aim of this thesis was to develop and pilot a self-help intervention about nutrition and physical activity for endometrial cancer survivors.

This PhD aimed to address the following questions:

1. What is the evidence for an association between health behaviours/obesity with survival in endometrial cancer survivors?
2. What is the evidence for an association between health behaviours/obesity with HRQoL in endometrial cancer survivors?
3. What are the health behaviours, nutritional status, and health beliefs of endometrial cancer survivors?
4. What are the attitudes, challenges, and needs of endometrial cancer survivors about diet and physical activity?
5. Can an existing self-help healthy eating and physical activity intervention program be adapted and tailored to endometrial cancer survivors?
6. Is it feasible to design a randomised controlled trial that will assess if the adapted programme is more effective than usual care in improving the HRQoL of endometrial cancer survivors?

Chapter 3 Obesity, diet, physical activity and endometrial cancer survival: A systematic review and meta-analysis

3.1 Introduction

In endometrial cancer survivors, factors such as stage, histological type, and deprivation level are associated with poorer survival (NCIN, 2013). Most survivors are diagnosed with type I endometrial cancer and at an early stage meaning that they have a good prognosis (NCIN, 2013). Still, the prevalence of inactivity, poor diet quality and obesity is considerably high (von Gruenigen et al., 2011), and these are widely known risk factors for overall mortality in the general population. According to a recent systematic review, lifestyle factors that seem to mostly account for endometrial cancer development include body fatness, glycaemic load, low physical activity, and low coffee intake (WCRF, 2013).

The association between lifestyle factors and survival after treatment is unclear. A systematic review of the literature on BMI and survival until 2011 yielded conflicting results; with only two out of twelve studies indicating significantly higher mortality in those

with a body mass index (BMI)>40kg/m^2 compared with those with a BMI<30kg/m^2 (Arem and Irwin, 2013). While the review followed a systematic methodology, the search strategy did not include grey literature, and this might have biased the results. Furthermore, many studies did not meet acceptable methodological standards, as acknowledged by the authors.

Studies published after 2011 have further investigated the link between obesity and endometrial cancer survival. An analysis of 1070 early-stage endometrial cancer survivors in the UK indicated that BMI did not affect overall survival three years post diagnosis (Crosbie et al., 2012). However, two large US prospective studies indicated that pre-diagnosis BMI is negatively associated with endometrial cancer survival five and ten years after diagnosis (Arem et al., 2013b, Arem et al., 2013a). These studies were included among 15 others in a recent meta-analysis that indicated a 1.66 (95% CI: 1.10, 2.51) increase in the odds ratio of mortality for the survivors with BMI≥40kg/m^2 compared with those in the normal category (BMI: 18.5 – 25kg/m^2) (Secord et al., 2016). There were no significant differences in mortality for the remaining BMI categories but a dose-response model demonstrated a significant 9.2% increase in mortality for every 10% increase in BMI. However, they did not examine the association between BMI and disease-specific or disease-free survival.

Given that diet and physical activity are the two primary drivers of energy balance, and, thus, of obesity, understanding their association with survival can provide vital hypotheses for examination in large-scale clinical trials. For example, the association between physical activity and mortality has shown a trend but was not associated with overall mortality in the fully adjusted models in two large studies (Arem et al., 2013b, Arem et al., 2014). Moreover, the relationship between diet and outcomes after endometrial cancer diagnosis remains largely unknown (McTiernan et al., 2010, Rock et al., 2012). However, the literature has not

been systematically examined for diet and physical activity in endometrial cancer survivors. Furthermore, other indices of energy balance such as weight change and body composition influence survival irrespective of BMI in other cancer survivors (Martin et al., 2013). The literature on these indices in endometrial cancer survivors is scarce but interpreting the BMI – survival association in the context of these data is vital, given that BMI is an imprecise obesity surrogate in cancer and elderly populations.

3.2 Aims

In light of mixed evidence and further studies published following the last review, the purpose of this study was to update the previous reviews on obesity and endometrial cancer survival and further explore the potential associations between nutrition, diet (food groups, dietary patterns), and physical activity with survival after endometrial cancer treatment.

3.3 Methods

3.3.1 Eligibility criteria

Studies were included if there was a distinct analysis of women diagnosed with endometrial cancer of any stage (Pecorelli, 2009, Creasman, 1990). Studies examining solely clear cell or papillary serous carcinomas as well as sarcomas (type II endometrial cancer) were excluded due to differences in morphology and prognosis (Felix et al., 2010). Survivors were defined as those after the end of primary or adjuvant therapy treatment with or without recurrent disease. Any study that investigated the associations between obesity, diet, physical activity and endometrial cancer survival was eligible. Variables were based on the WCRF breast cancer survivors systematic review protocol (WCRF, 2010) and are available in Appendix 1. However, criteria for assessing the exposure variables were not pre-defined (i.e.

comparisons). This was decided based on the wide scope of the literature review aiming to comprehensively capture any evidence linking the exposure variables with the outcomes, especially given the lack of clinical trials assessing these links. The original definitions of overall, disease-free, and disease-specific survival in each article were used. With the exception of specifying the comparison variables, the review followed the PRISMA guidelines for systematic reviews (Moher et al., 2009).

3.3.2 Identification of studies

The review included published studies and grey literature in all languages from 2011 until January 2014 for the associations between obesity and survival and from inception to January 2014 for the associations between diet, physical activity, and survival. Although I was not aware of any studies investigating diet, it was sensible to include it in the search. Studies on the association between BMI and survival before 2011 were identified from the previous reviews. Databases included EMBASE, MEDLINE via PubMed, PsycINFO, and Cochrane. Citations from included reports were scanned. An extended search to identify unpublished literature included contacting experts and manual searching of relevant conference proceedings. An experienced academic librarian assisted in the creation of the search protocol, which can be found in **Error! Reference source not found.**. Briefly, it included relevant terms for the following domains: obesity, body mass index, diet, energy balance, body composition, physical activity, and survival. An updated PubMed search was conducted in April 2016.

3.3.3 Study selection

Titles and, where available, abstracts were reviewed against inclusion criteria. For those that appeared to meet inclusion criteria, full texts were reviewed. Contact with the relevant

authors was not sought in the interest of time. Potential ambiguities for study inclusion were discussed with the supervisory team (MTK, AL) and resolved.

3.3.4 Data extraction and quality assessment

EndNote X7 and Microsoft Excel 2011 were used for data extraction. Data extraction forms (**Error! Reference source not found.**) were generated following the Centre for Reviews and Dissemination (CRD, 2009). Methodological quality was assessed through the SIGN checklists. Quality of reporting was based on STROBE guidelines for observational studies (von Elm et al., 2007). Data from studies identified in the previous literature reviews were also extracted from the original papers. While originally not planned, authors were contacted for clarifications to enhance data synthesis. Only five of them replied positively (Geels et al., 2012, Giugale et al., 2012, Gunderson et al., 2014, Linkov et al., 2015, Canlorbe et al., 2015).

3.3.5 Statistical analysis

The low methodological and reporting quality in most studies, the use of different BMI intervals, and the adjustment for different covariates rendered the quantitative synthesis of the data challenging. It was only possible to meta-analyse data with overall survival (all-cause mortality hazard ratios) as an outcome measure, as most studies reported BMI as a non-significant predictor of disease-free or disease-specific survival without reporting the relevant hazard ratios. While it was not possible to follow the same methodology with the previous meta-analysis (Secord et al., 2016), BMI was dichotomised assessing the extreme categories, or, alternatively, the closest possible approximation was used. For example, if a study had used the WHO BMI obesity categories in the analysis, only the hazard ratios between BMI categories 18.5-25 and $\geq 40 kg/m^2$ were compared. Hazard ratios for

continuous BMI were also included in the full model. The relevant hazard ratios and 95% confidence intervals (CIs) were pooled using a fixed or a random effects model. The latter weights each study based on its inverse variance. Heterogeneity between studies was assessed with the I^2 test (Higgins et al., 2003). In case of a value of $I^2 \geq 75\%$, indicating substantial heterogeneity, the random effects model was used. Publication bias was assessed through funnel plots, Egger's test, and Begg's test (Egger et al., 1997). The failsafe N test was used to assess if the entire effect was attributable to bias, and Duval and Tweedie's trim and fill method to adjust the combined hazard ratio, by imputing potentially missing studies in the model. The five sensitivity analyses included (a) removing the studies with continuous BMI and those that included overweight and obese in the same category; (b) including only the continuous BMI in the analysis; (c) including only the studies assessing pre-diagnosis BMI; (d) including the studies with high methodological quality using the dichotomised BMI; (e) including the studies with high methodological quality using continuous BMI. The level of statistical significance was set at $P<0.05$. Analyses were performed using Comprehensive Meta-analysis, v3.0 (Biostat).

3.4 Results

3.4.1 Details of included and excluded studies

Of the 5011 identified reports, 31 original studies and 14 previously reviewed studies (Arem and Irwin, 2013, Secord et al., 2016) were finally included. They are described in Table 3.1, Table 3.2, and Table 3.3. Of those 45 articles, 20 provided substantial information for the meta-analysis. The study selection process and the reasons for exclusion are presented in the flow diagram of Figure 3.1 PRISMA flow chart of the stages of the literature review. Only three studies (Arem et al., 2013a, Arem et al., 2013b, Crosbie

et al., 2012) were deemed of high methodological quality according to the SIGN checklist (Table 3.5).

3.4.2 Findings of the review

3.4.2.1 Overall survival

Of the 34 studies that reported an association between BMI and overall survival, 20 were included in the current meta-analysis (Figure 3.2). The follow-up time ranged from 1.1 to 12.3 years. Compared to participants with normal BMI, those with higher BMI had a significantly increased risk of all-cause mortality (HR_{random}: 1.05 (95% CI: 1.01, 1.10), P=0.016). When each study was removed from the analysis, the point estimates did not materially differ, ranging from 1.02-1.08, and they remained statistically significant except when the studies of (Arem et al., 2013b, Reeves et al., 2007) were removed. However, substantial heterogeneity was observed ($Q_{observed}$=115.3, $Q_{expected}$=20), with 84% of the observed variance to indicate differences in true effect sizes instead of sampling error.

In sensitivity analysis including the 11 studies comparing the extreme BMI categories, survivors with obesity had significantly higher all-cause mortality (HR_{random}: 1.42 (95% CI: 1.13, 1.79), P=0.002, I^2=76%) (Figure 3.3). When BMI was assessed as a continuous variable, the association with all-cause mortality became non-significant (Figure 3.4). Given the high heterogeneity in the above syntheses, further sensitivity analysis was confined to the studies of high-methodological quality. In those (Figure 3.5), higher BMI was positively associated with all-cause mortality in both dichotomous (HR_{fixed}: 1.95 (95% CI: 1.49, 2.56), P<0.001, I^2=0%) and continuous BMI models (HR_{fixed}: 1.16 (95% CI: 1.09, 1.23), P<0.001, I^2=61.6%). Further removal of the Crosbie et al study from the latter model for estimation of the association only in the long-term indicated a 19% (95% CI: 1.11, 1.26) increase in

all-cause mortality for every 1kg/m^2 increase in the BMI score (I^2=0%). Finally, analysing only the studies assessing BMI pre-diagnosis yielded even higher estimates (Figure 3.6).

On visual examination, the forest plot was skewed to the right indicating publication bias possibly due to the absence of studies with non-significant results (**Error! Reference source not found.**). This was confirmed by the Egger's test (*P*=0.01), but not the Begg's test (*P*=0.54), and was to be expected, as 11 of the 14 studies that did not provide sufficient data to be included in the meta-analysis showed a non-significant association between BMI and survival (Table 3.4). However, it is unclear how their inclusion would shift the estimates given their high risk of bias. Examining if the entire effect can be attributable to bias, the fail-safe test indicated that 127 studies with an effect of zero would need to be added in the model to render the combined HR non-significant. Due to the high heterogeneity, Orwin's test was not performed. Adjusting for the funnel plot asymmetry to the left using the trim and fill method, five imputed studies rendered the overall pulled effect non-significant ($HR_{random(adj)}$: 1.00 (95% CI: 0.99, 1.01)). In the sensitivity analysis of the high quality studies, there were no imputed studies in the trim and fill test, thus, the HR remained unchanged.

Adding to the BMI-survival association, one retrospective study reported better survival with weight gain less than 1kg compared to weight gain more than 1kg or weight loss at 6, 12 and 24 months ($p<0.05$) (El-Safadi et al., 2012). The results also showed that weight gain more than 1kg conferred better survival benefits in both normal weight and obese survivors compared with weight loss. The latter was associated with worse mortality regardless of weight status ($p<0.05$). On the other hand, sarcopenia (low muscle mass) was not associated with 3-year survival in a small cohort (N=112) (Kuroki et al., 2015).

3.4.2.2 Disease-Free and Disease-Specific Survival

Eighteen of the 22 studies examining disease-free survival showed no association with BMI, three showed a positive association and for one the direction of the association was unclear (Table 3.1). However, given the poor reporting of the HRs in most studies, a meta-analysis was not performed. One study demonstrated improved disease-free survival with weight gain less than 1kg compared with weight gain more than 1kg or weight loss at 24 months (El-Safadi et al., 2012). Furthermore, sarcopenia was associated with 4-times decreased disease-free survival (Kuroki et al., 2015) (Table 3.3).

Of the 18 studies assessing disease-specific survival, only the two with high methodological quality reported marginal associations with BMI (HR: 1.14 (1.01, 1.29) (Arem et al., 2013b) and HR: 1.17 (0.98, 1.40) (Arem et al., 2013a)). The rest of the studies revealed no association (Table 3.1 and Table 3.2).

3.4.2.3 Physical activity, diet, and survival

Conversely, the association between physical activity and overall survival was assessed in two studies indicating a negative but non-significant trend (Arem et al., 2013a, Arem et al., 2013b). In these two studies, physical activity did not seem to be associated with either disease-free or disease-specific survival (Table 3.2). Associations with diet and dietary intake biomarkers with survival outcomes were not reported in the literature. Only gamma-glutamyltransferase – a liver dysfunction biomarker that may be related with diet – has been shown to be a significant risk factor to survival after endometrial cancer treatment (Edlinger et al., 2013). No relevant non-English articles were identified.

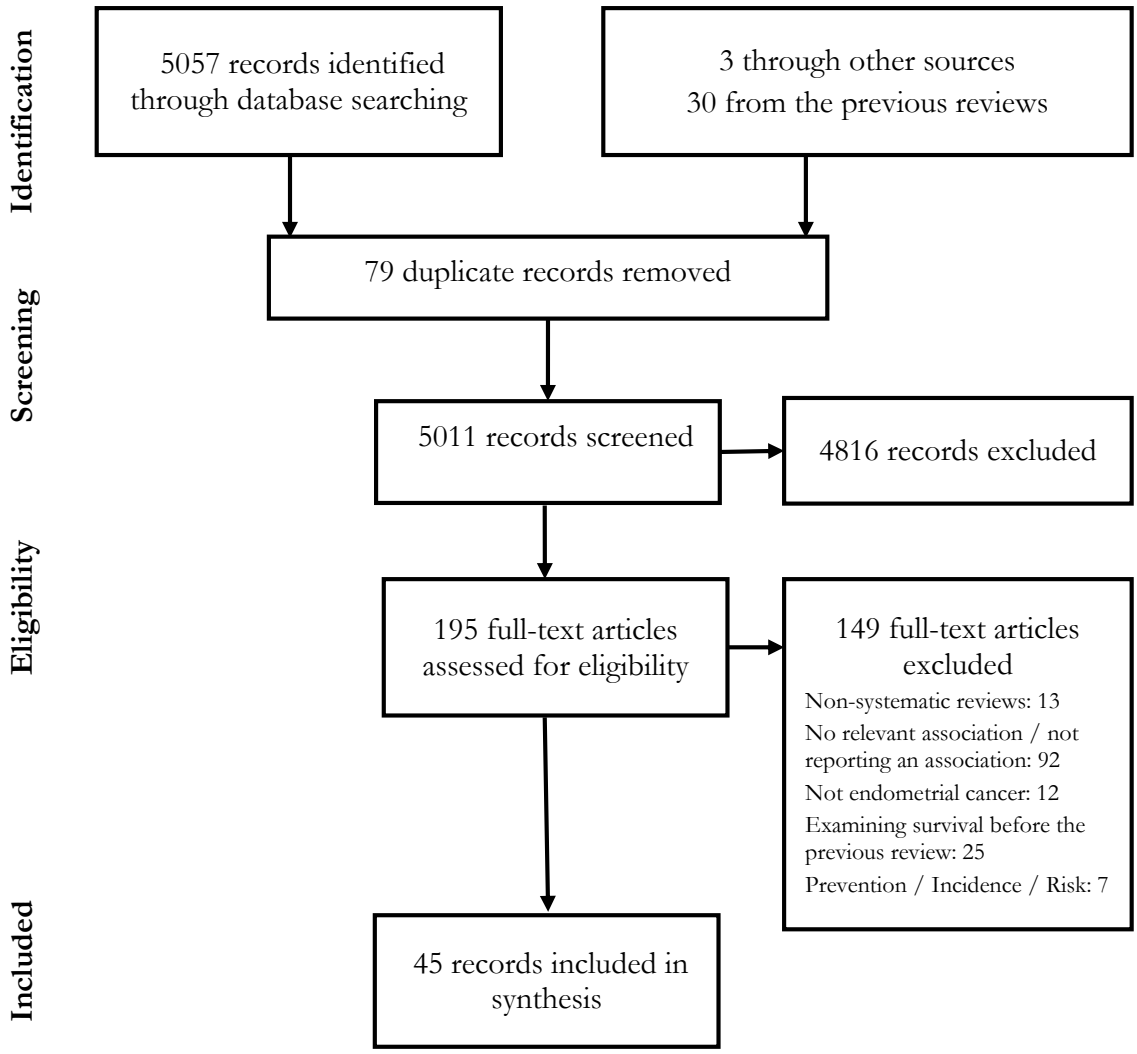

Figure 3.1 PRISMA flow chart of the stages of the literature review

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Table 3.1 Associations between BMI and survival outcomes

Reference	Study characteristics	Total N	Total deaths %	Overall survival (OS) BMI	HR	Total Recurrence %	Disease free survival (DFS)	Total EC deaths %	Disease specific survival (DSS)		Covariates included
(Crosbie et al., 2012)	Prospective FU: 2.9y Type I EC: 100% Age: 63.4±9.4y	893 (77% of total cases)	13%	<18.5 18.5–24.9 25.0–29.9 30.0–34.9 35.0–39.9 ≥40 BMI continuous	1.01 (0.13, 7.76) 1.00 1.00 (0.56, 1.79) 0.84 (0.44, 1.61) 0.62 (0.27, 1.42) 1.17 (0.49, 2.76) 0.96 (0.81, 1.14)	8.7%	1.68 (0.39, 7.13) 1.00 0.97 (0.59, 1.57) 0.81 (0.47, 1.39) 0.94 (0.51, 1.75) 1.17 (0.57, 2.39) 0.98 (0.86, 1.13)	NR	NR		Age, risk group, PS
(Trovik et al., 2012)	Retrospective / Prospective FU: 7.5y Type I EC: 91% Age: 66 (27–94)y	924	NR	<25 ≥25	1.00 0.86 (0.66, 1.11)	NR	NR	17.6%	Normal Overweight /Obese	1.00 0.79 (0.54, 1.14)	Age, parity, stage, grade, histology, MI, treatment
(Akbayir et al., 2012)	Retrospective FU: 4.9y Type I EC: 89% Age: 56.1±9.7y	346	8.7%	<25 25–30 >30	1.00 0.82 (0.15, 4.29) 0.55 (0.13, 2.34)	6.4%	1.00 1.92 (0.48, 7.50) 1.17 (0.41, 3.43)	7.7%	NR		Age, stage, grade, histology, hypertension, MI, LVSI, radiation
(Nicholas et al., 2012)	Retrospective FU: 4.5y Type I EC: ? Age: 48% >60y	490	NR	<25 25-39 >40	1.00 1.28 (0.77, 2.14) 0.98 (0.62, 1.57)	NR	NR	NR	NR		Univariate
(Rabischong et al., 2011)	Retrospective FU: 5.8y Type I EC: ?	207	NR	NS between non-obese / obese P=0.73 <30 ≥30	 88.5% (82-93) 90.3% (77-96)	NR	KM: NS between BMI categories *P*=0.70	NR	NR		NR

Reference	Study characteristics	Total N	Total deaths %	Overall survival (OS) BMI HR	Total Recurrence %	Disease free survival (DFS)	Total EC deaths %	Disease specific survival (DSS)	Covariates included
(Baek et al., 2014)	Retrospective FU: 6.1y Type I EC: 82% Age: 51y	278	4.3%	NS between BMI groups *P*=0.436	7.9%	NS between BMI groups *P*=0.313	NR	NR	No Cox PH model
(Ko et al., 2014)	Retrospective FU: approx. 2y Type I EC: 100% Age: approx. 61y	1144	NR	NS BMI continuous HR: 0.99 (0.96 - 1.01)	NR	NS BMI continuous HR: 0.98 (0.96-1.00)	NR	NR	Age, race, grade, stage, BMI, diabetes, adjuvant therapy
(Todo et al., 2014)	Retrospective FU: 6.2 y Type I EC: 87% Age: 58y	716	NR	NS between BMI<30/>30 *P*=0.50	NR	NR	NR	Non-obese 1.00 Obese 0.88 (0.51, 1.53)	Age, stage, grade, hysterectomy, lymphadenectomy, chemotherapy
(Gayar et al., 2013)	Retrospective FU: 4.3y Type I EC: 100% Age: 60y	949	NR	Cox PH - BMI P=0.046, direction of association NR, HR NR	8%	NS, HR NR		NS, HR NR	Age, race, stage, grade, LUSI, LVSI, treatment
(Nevadunsky et al., 2014)	Retrospective FU: NR Type I EC: 100% Age: 61.9y	522	NR	NS Log-rank: *P*=0.47	NR	NR	NR	NR	Univariate - No Cox PH model
(Linkov et al., 2015)	Retrospective FU: Max 10y Type I EC: 100% Age: 36.5% 66-75y	192	30.7%	Positive association, higher OS in the BMI≥40 group, Log-rank: *P*=0.05	12.5%	Positive association, higher DFS in the BMI≥40 group, Log-rank *P*=0.03	9.4%	NS log-rank *P*=0.86	Univariate - No Cox PH model
(Uccella et al., 2011) Abstract only	Retrospective Type I EC: ?	192	NR	BMI NS	NR	BMI NS	NR	NR	NR

Reference	Study characteristics	Total N	Total deaths %	Overall survival (OS) BMI HR	Total Recurrence %	Disease free survival (DFS)	Total EC deaths %	Disease specific survival (DSS)	Covariates included
(Ouldamer et al., 2013) Abstract only	Retrospective Type I EC: ?	192	NR	NS between BMI groups *P*=0.54	NR	NR	NR	NR	NR
(Park et al., 2014b)	Retrospective FU: 5.3y Type I EC: 100% Age: 51.5y	213	NR	NR	11.7%	BMI<30: 86.7% vs. BMI>30: 91.7%, *P*=0.249		BMI<30: 91.4% vs. BMI>30: 95.4%, *P*=0.256	Univariate
(Gunderson et al., 2014)	Prospective FU: 4.9y Type I EC: 77% Age: 62y	2596	NR	BMI negatively predicted OS *P*=0.0157 <30.0 1.00 ≥30.0 1.51 (1.10, 2.09)	9.8%	NS between BMI groups *P*=0.461 <30.0 1.00 ≥30.0 1.39 (1.04, 1.84)	NR	NS P=0.468 <30.0 1.00 ≥30.0 1.29 (0.80, 2.08)	Age, race, performance status, adjuvant therapy, recurrence risk group
(Acharya et al., 2016)	Retrospective FU: 2.5y Type I EC: 88% Age: 62y	43	46.5%	NS BMI continuous HR: 0.99 (0.97 - 1.202)	NR	NR	NR	NR	Univariate
(Ruterbusch et al., 2014)	Retrospective FU: 12.3y Type I EC: 75% (White only) Age: approx. 64y	356	53.9%	NS between BMI groups *P*=0.82 <30.0 1.00 ≥30.0 1.04 (0.75, 1.43)	NR	NR	11.8%	NS *P*=0.74 <30.0 1.00 ≥30.0 0.89 (0.44, 1.79)	Age and year at diagnosis, stage, grade, histology, treatment type
(Menderes et al., 2014)	Retrospective FU: 2.4y Type I EC: 81% Age: 64y	364	NR	NS between BMI groups *P*=0.28	0.1%	BMI<30 had shorter DFS compared to BMI≥30, HR NR	NR	NR	Univariate
(Giugale et al., 2012)	Retrospective FU: 2y Type I EC: 78.1% Age: 58y	577	4.7%	NS between BMI groups *P*=0.677	11.7%	NS between BMI groups *P*=0.066	2.9%	NS between BMI groups *P*=0.99	Univariate

Reference	Study characteristics	Total N	Total deaths %	Overall survival (OS) BMI	HR	Total Recurrence %	Disease free survival (DFS)	Total EC deaths %	Disease specific survival (DSS)	Covariates included
(Long et al., 2012)	Retrospective FU: 3y Type I EC: 100% Age: 66y	124	17.9%	NR		7.2%	HR 1.08 (0.95, 1.23)	5.2%	NR	Univariate
(Geels et al., 2012)	Retrospective FU: 5.1y Type I EC: 100% Age: 62y	489	6.2%	NR		4.3%	<30.0 1.00 ≥30.0 0.94 (0.88, 0.99)	1.4%	NR	Univariate
(Canlorbe et al., 2015)	Retrospective FU: 2.25y Type I EC: 87% Age: approx. 65y	729	9.7%	NR		13.9%	<30.0 1.00 ≥30.0 1.03 (0.67, 1.60)	NR	NR	Age, histology, LVSI status, adjuvant therapy, nodal staging
(Lee et al., 2012)	Retrospective FU: 4.7y Type I EC: 85.9% Age: 51y	248	6.5%	NR		10.5%	NS, HR NR	NR	NS, HR NR	Univariate
(Ni et al., 2014) Abstract only	Retrospective FU: NR Type I EC: NR Age: NR	256	24.2%	NR		NR	NR	NR	NS P=0.468	NR
(Lino-Silva et al., 2013)	Retrospective FU: 3.2y Type I EC: 98% Age: 40% >60y	147	NR	NR		NR	NR	11.5%	Cox-PH NS, HR NR, KM: *P*=0.830	Age, histology, grade
(Smits et al., 2013)	Retrospective FU: 2.5y Type I EC: 100% Age: 70y	158	NR	NR		9.5%	NS recurrence rates between BMI groups.	NR	NR	
(Chia et al., 2007)	Unclear FU: 9.3y	745	22.3%	Continuous BMI <25	1.02 (0.99, 1.04) 1.00	NR	NR	5.6%	Continuous HR: 1.03 (0.98, 1.08)	Age, stage, menopause,

Reference	Study characteristics	Total N	Total deaths %	Overall survival (OS) BMI	HR	Total Recurrence %	Disease free survival (DFS)	Total EC deaths %	Disease specific survival (DSS)		Covariates included
	Type I: NR Age: NR BMI pre-diagnosis			25.0–29.9 ≥30.0	1.20 (0.80, 2.00) 1.60 (1.00, 2.50)				<25 25.0–29.9 ≥30	1.00 1.1 (0.4, 2.7) 2.0 (0.8–5.1)	diabetes, smoking, oral contraceptive, parity, PMH
(Gates et al., 2006)	Retrospective FU: 5y Type I: 100% Age: 64y	99	11.1%	<25 >25	1.00 5.4 (0.49, 59.0)	NR	NR	NR	NR		Stage, race, parity, PR, HER-2/neu
(Jeong et al., 2010)	Retrospective FU: NR Type I: 100% Age: 52y	937	NR	<23 23.0-24.9 ≥25	1.00 0.93 (0.37, 2.29) 0.87 (0.41, 1.83)	NR	NR	NR	NR		Age, menopause, stage, grade, treatment, LVSI
(Kodama et al., 2005)	Retrospective FU: 4.5y Type I: 93% Age: 57y	242	NR	NS between BMI groups *P*=0.07		13.2%	NS between BMI groups, *P*=0.34	NR	NR		Univariate
(Martra et al., 2008)	Retrospective FU: 3.2y Type I: 89% Age: 62% <60y	766	15.7%	<30 ≥30	1.00 1.04 (1.01, 1.07)	16.2%	Higher DFS with higher BMI only when nodes were not sampled *P*=0.03	6.4%	NS between BMI groups irrespective of node status		For OS: Age, stage, grade, histology, MI, treatment
(Mauland et al., 2011)	Retrospective FU: 4.9y Type I: 86% Age: (In quintiles)	905	35.6%	BMI continuous: 1.02 (1.00–1.04)		NR	NR	19.2%	BMI continuous <25 ≥25	HR: 1.01 (0.98–1.04) 1.00 1.07 (0.73, 1.32)	Age, stage, histology, grade
(Modesitt et al., 2007)	Retrospective FU: 1.1y Type I: 50% Age: 10% <50y Stages III-IV only	949	81.3%	<25 25.0–29.9 30.0–39.9 ≥40	1.00 0.96 (0.69, 1.33) 1.33 (0.96, 1.84) 1.86 (1.16, 2.99)	NR	1.00 0.93 (0.66, 1.27) 1.23 (0.92, 1.66) 1.22 (0.76, 1.94)	NR	NR		Age, race, PS, stage, grade, histology, treatment
(Munstedt et	Retrospective	977	NR	BMI continuous		NR	NR	NR	NR		Age, stage,

Reference	Study characteristics	Total N	Total deaths %	Overall survival (OS) BMI	HR	Total Recurrence %	Disease free survival (DFS)	Total EC deaths %	Disease specific survival (DSS)	Covariates included
al., 2008)	FU: 6.2y Type I: 59% Age: 68y			HR: 0.98 (0.95–1.00)						grade
(Reeves et al., 2007)	Prospective FU: 7y Type I: NR Age: Approx. 56y BMI pre-diagnosis	2657	8.9%	BMI per 10 units <22.5 22.5-24.9 25.0–27.4 27.5–29.5 ≥30	2.46 (1.78, 3.39) 0.81 (0.57, 1.17) 1.00 1.09 (0.82, 1.45) 1.21 (0.85, 1.71) 2.28 (1.81, 2.87)	NR	NR	NR	NR	Age, region, SES, parity, PA, smoking, alcohol
(Temkin et al., 2007)	Retrospective FU: NR Type I: 84% Age: 63y	442	37.8%	BMI continuous HR: 0.99 (0.97–1.05)		NR	NS, HR NR	29.6%	NS, HR NR	Age, stage, grade, race, treatment
(von Gruenigen et al., 2006)	Retrospective FU: 5.4y Type I: Age: 39% 60-69y	380	16.1%	<30 30.0-39.9 ≥40	1.00 1.47 (0.81, 2.67) 2.76 (1.20, 6.33)	11.6%	<30 1.00 30.0-39.9 0.98 (0.51, 1.86) ≥40 0.41 (0.09–1.83)	6.6%	NR	Age, stage, grade, race, histology, MI, PS, LVSI, treatment
(Anderson et al., 1996)	Retrospective FU: 4.6y Type I: 85% Age: 62y	488	20.3%	Cox PH—no association, HR NR; KM: positive association between continuous BMI and survival *P*=0.06		16.4%	DFS positively associated with continuous BMI *P*=0.01, HR NR	NR	NR	MI, stage
(Everett et al., 2003)	Retrospective FU: 2.3y Type I: 78.5% Age: 60y	396	12.9%	NR # Deaths NS between BMI groups *P*=0.18		10.6%	NR # Recurrence NS between BMI groups *P*=0.07	4.5%	# deaths NS between BMI groups	Univariate
(Studzijnski and Zajewski, 2003)	Retrospective FU:5y Type I: 77% Age: 60y	121	NR	Highest % 5-year survival for BMI 25–29 group, HR NR, Obese had longer survival than non-obese (87.4% vs. 73.4%) *P*=0.05		NR	NR	NR	NR	Univariate

Age: Reported in mean±SD, median (range), or %, NR: Not reported, NS: Not statistically significant, FU: Follow-up in years (mean or median), MI: Myometrial invasion, HRT: Hormone replacement therapy, RH: Reproductive history, PA: Physical activity, PS: Performance status

Table 3.2 Effects of exposure variables on mortality

Reference	Study characteristics	Total N	BC Measure	Diet measure	PA measure	All-cause Mortality	Disease-specific mortality	Covariates included
(Edlinger et al., 2013)	Prospective FU: 11.9 years Type I EC: 78% Age: 61.0±9.8y	242 of 318 cases (76%)	BMI measured	Pre-diagnostic levels Blood pressure, triglycerides, total cholesterol, glucose, GGT, serum uric acid	NR	Log_{10}GGT 2.37 (1.01, 5.56) The rest biomarkers were not significant	Log_{10}GGT 3.35 (1.12, 10.03) The rest biomarkers were not significant Log-rank test GGT P=0.02 GGT <18 1.00 18-36 2.03 (0.84, 4.93) >36 3.03 (1.10, 8.30)	Age, examination year, FIGO, histology, BMI, hypertension, log_{10}TGA, total cholesterol, glucose, serum uric acid
(Arem et al., 2013a)	Prospective FU: 5.2 years Type I EC: 100% for BMI and 84% for Physical activity Age at enrolment: 63.6±6.9y	983 of 1362 cases (72%)	BMI measured at diagnosis	Food records, food frequency questionnaires, 24-hour dietary recalls	Usual frequency of walking outside the home for >10 minutes without stopping MET h/wk	134 deaths Continuous BMI: 1.20 (1.07, 1.35) Physical activity MET h/week 0 1.00 0-<11.26 0.75 (0.51, 1.10) ≥11.26 0.93 (0.77, 1.13)	51 deaths Continuous BMI: 1.17 (0.98, 1.40) 1.00 0.51 (0.26, 1.01) 1.05 (0.79, 1.38)	Age, tumour grade and stage, age at menarche, time from baseline measures to endometrial cancer diagnosis
(Arem et al., 2013b)	Prospective FU: 10 years Type I EC: 89% Age at diagnosis: 88% >60y	1400 for BMI analysis (95%) 875 for physical activity analysis (60%) of 1466 cases	Self-reported weight and height pre-diagnosis	Diet History Questionnaire	NIH-AARP Physical activity Questionnaire (non-validated) Leisure time moderate-to-vigorous intensity physical activities h/wk	299 deaths Continuous BMI1.18 (1.09, 1.27) Normal 1.00 Overweight 1.59 (1.12, 2.25) Obese I 1.73 (1.20, 2.50) Obese II 2.23 (1.53, 3.23) 187 deaths Physical activity Never/rarely 1.00 <1 h/w 1.16 (0.71, 1.90) 1-3 h/w 0.68 (0.43, 1.09) 4-7 h/w 0.92 (0.58, 1.47) >7h/w 0.83 (0.51, 1.36)	133 deaths Continuous BMI 1.14 (1.01, 1.29) 1.00 1.26 (0.74, 2.15) 1.80 (1.05, 3.08) 1.79 (1.00, 3.21) 81 deaths 1.00 1.51 (0.72, 3.17) 0.54 (0.25, 1.20) 1.16 (0.56, 2.38) 1.01 (0.49, 2.09)	Tumour grade and stage, surgery, chemotherapy, race, family history of breast cancer, diabetes and smoking Tumour grade and stage, surgery, chemotherapy, race, family history of breast cancer, diabetes and smoking and continuous BMI

BC: Body composition, GGT: gamma-glutamyltransferase, PA: Physical activity, NIH-AARP: National Institute of Health, American Association of Retired Persons

Table 3.3 Effects of other body composition measures on overall and disease-free survival

Reference	Study characteristics	Body composition measure	Total N	Total deaths %	Overall survival (OS)	Total recurrence %	Disease free survival (DFS)	Covariates included
(El-Safadi et al., 2012)	Retrospective FU: 7.2y Type I EC: ? Age: 66.9±9.6y	Weight change	705	NR	KM: Better survival with weight gain <1kg vs. weight gain >1kg vs. weight loss <1kg vs. weight loss >1kg in 6 mo, 12 mo and in 24 mo, Log-rank: *P*=0.007	NR	KM: Better survival with weight gain <1kg vs. weight gain >1kg vs. weight loss <1kg vs. weight loss >1kg, Log-rank = 12.1, *P*=0.007	Stage, grade in DFS analysis
(Kuroki et al., 2015)	Retrospective FU: 2.7y Type I EC: 72% Age: 65.9±10.4y	Sarcopenia defined as <4.33cm² cross-sectional area of psoas muscle from CT scan	122	NR	Log-rank P=0.25 HR: 1.98 (0.81-4.86)	13.9%	Log-rank: *P*=0.02 HR: 3.99 (1.42 – 11.3)	Race, BMI, lymphocyte count, histology

Age: Reported in mean±SD, NR: Not reported, FU: Follow-up in years (mean or median)

Table 3.4 Summary of results by number of studies

	Association between BMI and		
	Overall survival	Disease-free survival	Disease-specific survival
Non-significant	24	18	17
Positive	7	3	0
Negative	2	0	1
Unclear	1	1	0
Total	34	22	18

Table 3.5 Methodological quality in cohort studies with survival outcomes

SIGN Methodological Quality (Yes=1, No=0, Can't say=3) High quality (++) Acceptable (+) Unacceptable (-)		Arem et al. (2013a)	Arem et al. (2013b)	Crosbie et al. (2012)	Edlinger et al. (2013)	Lino-Silva et al. (2013)	Geels et al. (2012)	Akbayir et al. (2012)	Ruterbusch et al. (2014)	Mauland et al. (2011)	Ko et al. (2014)	Gunderson et al. (2014)	Reeves et al. (2007)	von Gruenigen et al. (2006)	Nicholas et al. (2012)	Trovik et al. (2012)	Menderes et al. (2014)	Smits et al. (2013)	El-safadi et al. (2012)	Rabischong et al. (2012)	Gayar et al. (2012)	Acharya et al. (2016)	Lee et al (2012)
2.1	How well was the study done to minimise the risk of bias or confounding?	++	++	++	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	1	1	1	1	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

SIGN Methodological Quality (Yes=1, No=0, Can't say=3) High quality (++) Acceptable (+) Unacceptable (-)		Baek et al. (2014)	Ni et al. (2014)	Canlorbe et al. (2014)	Todo et al. (2014)	Park et al. (2014)	Nevadunsky et al. (2014)	Linkov et al. (2015)	Kuroki et al. (2015)	Long et al. (2012)	Giugale et al. (2012)	Chia et al. (2007)	Gates et al. (2006)	Jeong et al. (2010)	Kodama et al. (2005)	Martra et al, (2008)	Modesitt et al. (2007)	Munstedt et al. (2008)	Everett et al. (2003)	Temkin et al. (2007)	Anderson et al. (1996)	Studzinski et al. (2003)
2.1	How well was the study done to minimise the risk of bias or confounding?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

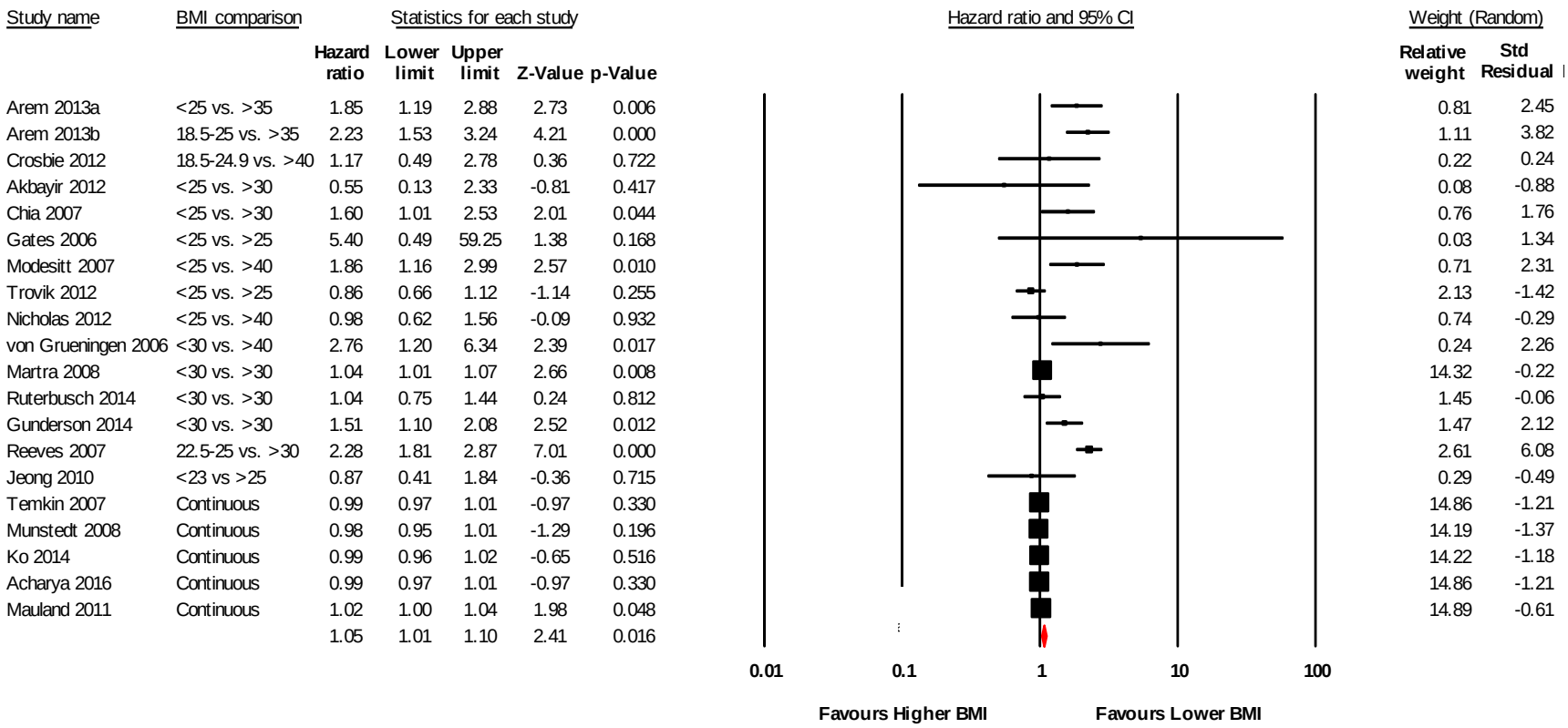


Figure 3.2 Association between BMI and all-cause mortality

The diamond denotes the pooled random effect. Box sizes (with 95% error bars) are proportional to their weight in the analysis (inverse of variance).

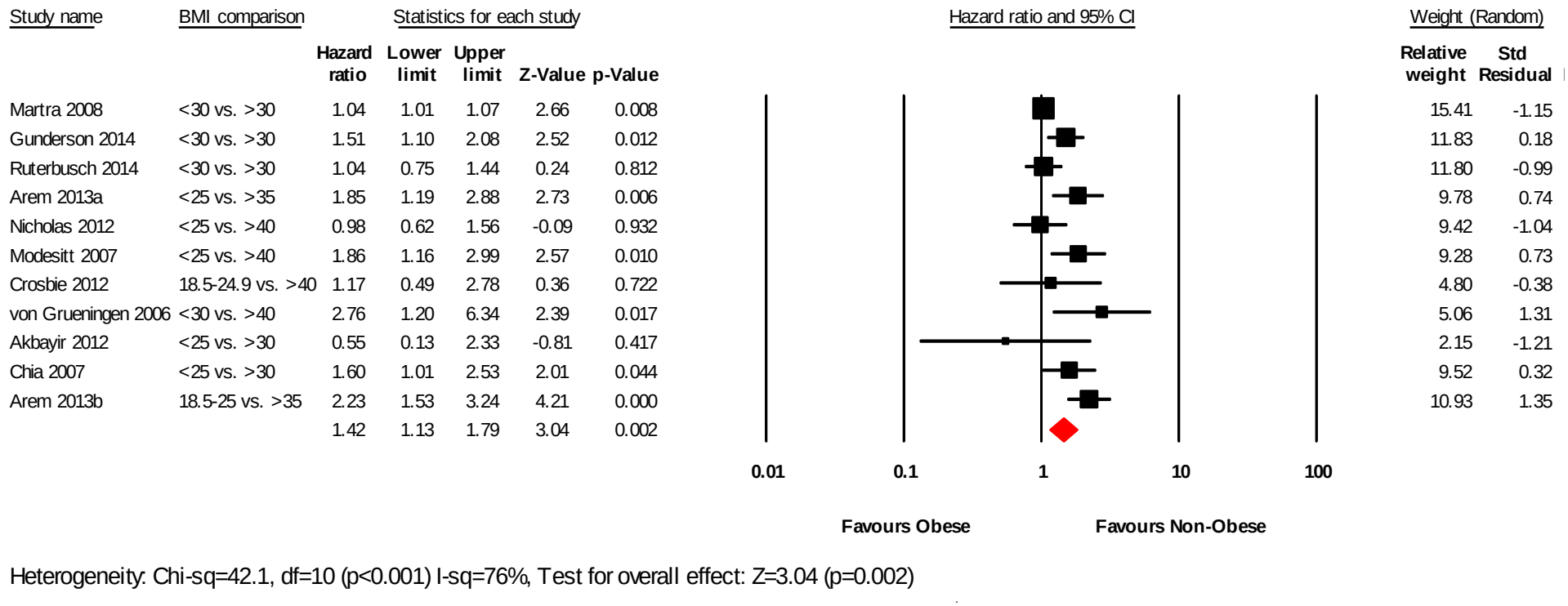


Figure 3.3 Association between extreme BMI categories and all-cause mortality

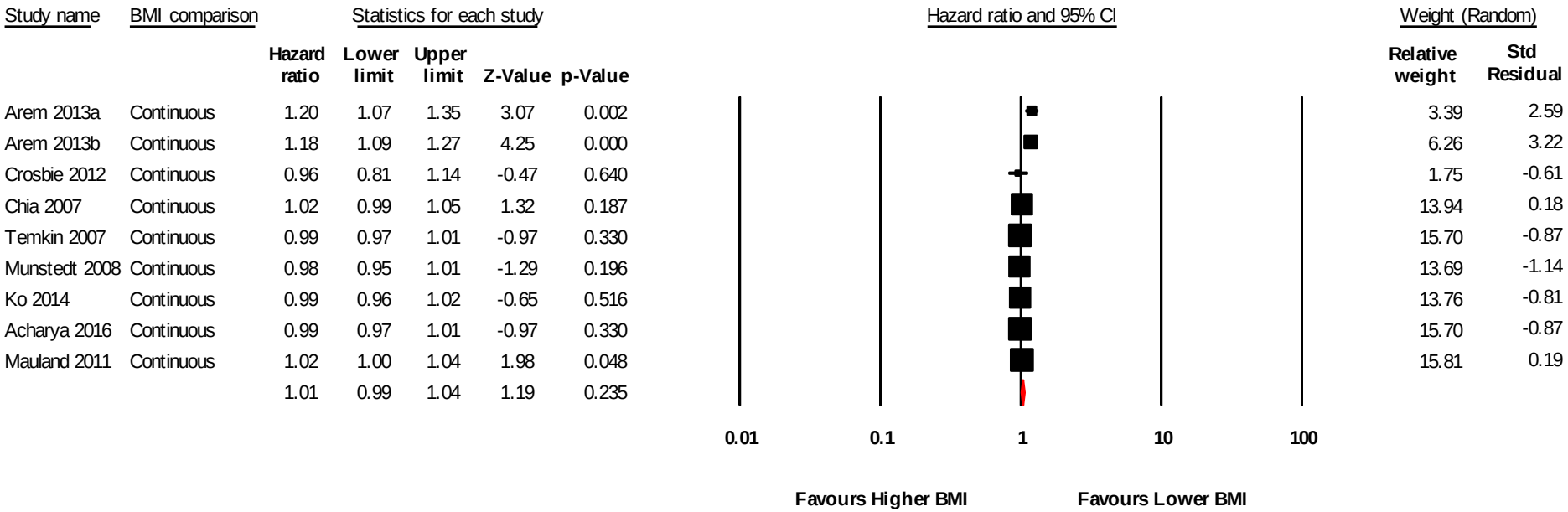
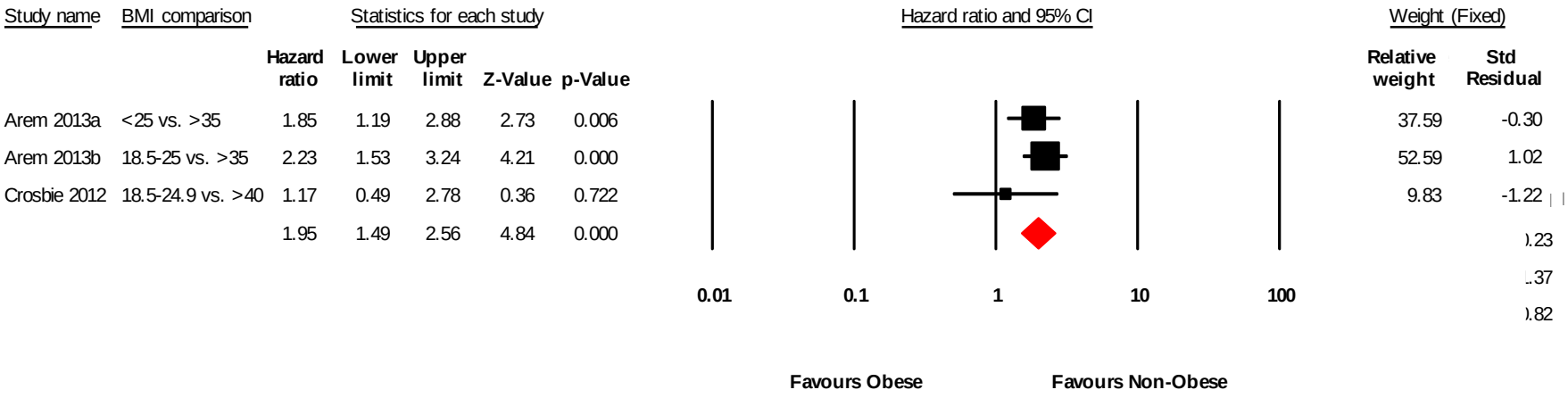


Figure 3.4 Association between continuous BMI and all-cause mortality



Heterogeneity: Chi-sq: 1.89, df=2 (p=0.39), I-sq=0%, Test for overall effect: Z=4.84 (p=<0.001)

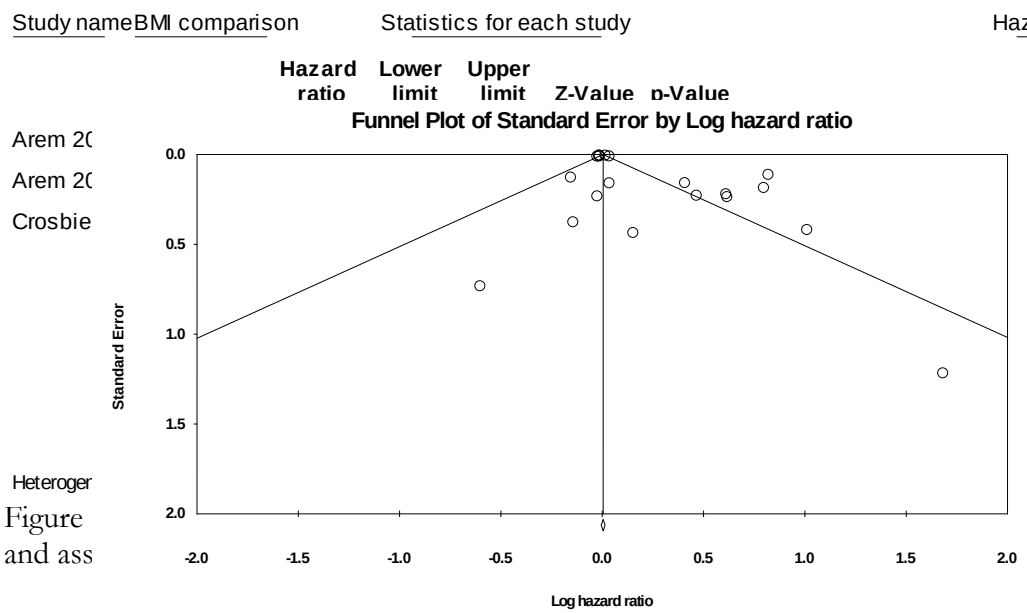


Figure 3.7 Funnel plot of standard error by log hazard ratio in the meta-analysis (full model)

Figure ... the studies with high methodological quality (above) and ass... h methodological quality (below)

3.5 Discussion

After merging the current results with the studies identified in the previous reviews (Arem and Irwin, 2013, Secord et al., 2016), twenty-four, seven, and two studies showed a non-significant, positive, or negative association between BMI and survival, respectively. Given the substantial heterogeneity of the meta-analysed studies, the analysis was confined to those studies with low risk of bias. It suggested a 9-23% higher risk of death with each 1kg/m^2 increase in BMI with the risk increasing to 11-26% five to ten years post-diagnosis. Low quality evidence suggested that BMI is not associated with either disease-free or disease-specific survival. One study reported improved survival with weight gain less than 1kg after diagnosis.

Given the low methodological and reporting quality and the high heterogeneity, interpretation of the synthesis of the literature remains challenging. The current point estimate of the analysis of dichotomous BMI in high-quality studies (HR: 1.95 (95% CI: 1.49, 2.56)) is somewhat higher and tighter than that reported in the previous meta-analysis (OR: 1.66 (95% CI: 1.10, 2.51 comparing BMI≥40 vs. BMI<25)) (Secord et al., 2016). In their full model, the authors also reported a high, but non-quantified, heterogeneity among the studies, but did not search in the grey literature, and could not quantify publication bias. Further differences include the exclusion from the current analysis of the studies of Calle et al and Bjorge et al (Calle et al., 2003, Bjorge et al., 2010), given that they reported disease-specific survival rather than overall survival and the analysis was on all uterine malignancies rather than endometrial cancer. The studies of (Kodama et al., 2005, Rabischong et al., 2011, Mauland et al., 2011) were also excluded, as the HR between BMI categories could not be verified in the crosscheck of the original articles. As the current review was initiated in 2013 and, therefore, included studies since 2011, the omission of

some studies in the previous meta-analysis was notable, such as those of (Nicholas et al., 2012) and (Trovik et al., 2012). Both the different statistical meta-analytic methods and publication bias might account for discrepancy in the dispersion of the effect estimates, given the high number of published studies with non-significant results identified in the current review that could not be meta-analysed given their poor quality of reporting.

Therefore, interpretation of this data is challenging primarily because of issues of reverse causation that arise when examining the relationship between BMI as a proxy of obesity and survival in elderly populations (see Tables for survivors' age in the reviewed studies). Specifically, illness may cause changes in weight status (i.e. weight loss) rather than weight status causing illness. This can blunt the effect of BMI as an obesity proxy on survival and it was apparent when analysis was confined to studies assessing BMI at diagnosis. This methodological issue has been previously reviewed (Manson et al., 2007). A recent meta-analysis of BMI and all-cause mortality in adults older than 65 years has shown a U-shaped relationship, with a BMI of 27.5kg/m^2 demonstrating the lowest risk for all-cause mortality (Winter et al., 2014). Furthermore, older men who were both sarcopenic (defined as low muscle mass) and obese (defined by waist circumference) had the highest all-cause mortality (Atkins et al., 2014).

In endometrial cancer survivors, the only study assessing weight changes (El-Safadi et al., 2012) is in line with evidence from the general elderly population demonstrating that weight stability predicts lower mortality (Bamia et al., 2010). In the cancer survivorship context, these weight changes possibly indicate pre-cachexia, ill- and age-related influences. On the one hand, the sparse existing evidence does not support the presence of cachexia in this population, as survivors seem to restore their body weight and muscle mass after treatment (Bruning et al., 1985). On the other hand, a small study indicated that 22% of survivors had sarcopenic obesity (low muscle mass and high fat mass) and indicated a

negative association between sarcopenia and disease-free survival (Kuroki et al., 2015). The negative impact of reduced muscle mass and strength on physical function and survival in older age, including cancer survivorship, is well established (Kalyani et al., 2014). Thus, (annualised) weight changes together with body composition indices (e.g. waist-to-hip ratio) and objective measures (e.g. computed tomography) could provide a clearer picture of the link between adiposity and survival by complementing BMI in future studies. Randomised controlled trials in cancer survivors have indicated positive metabolic changes after intentional weight loss (Reeves et al., 2014).

Furthermore, depending on cancer site, stage, and treatment, survivors may experience cachexia and unintentional weight loss; generally signs of worse prognosis. Prospective studies in breast cancer survivors (Bradshaw et al., 2012, Caan et al., 2012) demonstrate that both weight loss and weight gain are associated with lower survival compared to weight maintenance. While these studies could not differentiate between intentional and unintentional weight loss, it could be presumed that the associations might have arisen because of unintentional weight loss. An analysis of 8,160 cancer survivors, most of which had been diagnosed with advanced cancer, showed that survivors with BMI $\geq$ 25.0 kg/m^2 and stable weight had the longest survival (Martin et al., 2014).

Given the aforementioned limitations of BMI at diagnosis, the use of pre-existing BMI may reduce the confounding of pre-existing disease and increase the validity of any found association (Manson et al., 2007). Indeed, the analysis of the three studies assessing pre-diagnosis BMI produces the highest point estimates for all-cause mortality. These were much higher than those in the general population (Tobias and Hu, 2013). The increased mortality was primarily explained by cardiovascular events rather than endometrial cancer deaths in ten years in one of the studies (Arem et al., 2013b), indicating the high potential for disease prevention (Estruch et al., 2013).

Most studies performed multivariate analyses accounting for age and stage of the cancer, two factors that are strongly associated with both BMI and survival, as reported in the reviewed papers. However, limitations of the reviewed studies include lack of power, relatively short follow-up periods, various confounding adjustments in the multivariate models and lack of standard BMI cut-offs in some studies. The short follow-up period (2.9 years) in one of the well-conducted studies (Crosbie et al., 2012) might be the reason for lack of association between BMI and survival in this study, given than early-stage survivors have greater than 90% 5-year survival and 75% 10-year survival, and most survivors die from cardiovascular disease (Ward et al., 2012). Future robust studies with long-term follow-up would be expected to confirm the sensitivity analysis of the high quality studies with long-term follow-up. Notably, most studies were retrospective and BMI was abstracted from medical records. Moreover, most studies did not control for smoking and co-existing chronic diseases (Manson et al., 2007).

The trend towards better survival and physical activity before diagnosis agrees with extensive mechanistic and epidemiological evidence of the protective effects of physical activity (Gremeaux et al., 2012). Exercise seems to exert positive changes in survival-related biomarkers in cancer survivors (Ballard-Barbash et al., 2012). However, no study until now has assessed the independent effect of diet on endometrial cancer survival. The positive association between gamma-glutamyltransferase (a liver dysfunction biomarker) and mortality points towards better survival with improved metabolic profile and lifestyle factors associated with this biomarker, for example alcohol consumption, diabetes and obesity. Dietary patterns have been extensively studied regarding overall disease prevention (Katz and Meller, 2014), as well as cancer survival (Richman et al., 2013). Dietary behaviours are notoriously complex to measure but accounting for those in the models will

provide a firmer understanding of the link between nutritional status (including obesity) and health outcomes in endometrial cancer survivors.

The high prevalence of poor diet quality, and low activity levels are established risk factors for cardiovascular disease; the leading cause of death in this population (Ward et al., 2012). Therefore, future research should address the longitudinal effect of these modifiable factors after cancer diagnosis and explore their relationships with metabolism, genetics, treatment exposure, environment, and outcomes.

Strengths of the review encompass the comprehensive literature search including grey literature, no language restriction, contact with authors, and detailed collection and rigorous analysis of the data. While it was only possible to include the referent and one comparison BMI group in the synthesis, which substantially limits the sample size, data from the continuous BMI analysis support a dose response relationship. Generalizability of the findings is hampered because most studies did not report socio-demographic data. Based on the available data, most participants were white and of high education level and, therefore, the results may not be applicable to the rest of the endometrial cancer survivors, who are often of low socio-economic status (NCIN, 2013).

3.5.1 Conclusions

While the relationship between BMI and overall survival remains hard to disentangle, the current analysis suggests an inverse relationship between BMI and long-term overall survival. Furthermore, BMI does not appear to be associated with disease-specific or disease-free survival from endometrial cancer. Cardiovascular disease seems to be the primary long-term cause of death in this population that has high survival rates. Weight stability after diagnosis and body composition might be more important than BMI per se, although more data are needed to support this conclusion. This primarily lies in the

limitations of BMI as a proxy of adiposity in this population. Future research should focus on more reliable measures of body composition accounting for diet and physical activity; its two primary determinants. Examining intermediate outcomes that can be of similar importance as survival for both patients and policy makers (DoH, 2010), such as health-related quality of life (HRQoL), may provide further insight for intervention development. These are further explored in Chapters 4, 7, and 8.

Chapter 4 Obesity, diet, physical activity and health-related quality of life in endometrial cancer survivors: A systematic review

4.1 Quality of life in endometrial cancer survivors[4]

Chapter 2 presented intervention trials aiming to improve the persistent adverse physical, psychological, social, and spiritual effects that further compromise the health-related quality of life (HRQoL) of most cancer survivors (Miller et al., 2008). Following the identification of a potential survival advantage in survivors without obesity presented in 0, this chapter

[4] This chapter is an updated version of a previously published literature review Koutoukidis, D. A., Knobf, M. T. & Lanceley, A. 2015a. Obesity, diet, physical activity, and health-related quality of life in endometrial cancer survivors. *Nutr Rev,* 73**,** 399-408. The update expands the literature search chronologically while maintaining the original methodology.

will focus reviews the literature on the association between HRQoL with obesity, diet and physical activity in endometrial cancer survivors.

HRQoL can be conceptually defined as subjective assessments of physical well-being and symptoms (e.g. functional activities, fatigue, pain), psychological well-being (e.g. anxiety, depression), social well-being (e.g. family distress, work), and spiritual well-being (e.g. uncertainty, hope) (Hewitt et al., 2006). This is because HRQoL has no commonly accepted definition but it is broadly accepted as a multi-dimensional, self-rated measure of well-being (Montazeri et al., 1996). The case of endometrial cancer survivors is no exception, as cancer and its treatment negatively affect many aspects of their life (Penson et al., 2006).

Most patients will receive surgical treatment. Depending primarily on the stage and grade of the disease, chemotherapy, radiotherapy, and/or hormone therapy might also be part of the treatment plan (NCIN, 2013). All types of treatment may lead to fatigue or pain. Sixty nine per cent of patients with early stage disease (Stage I and II) will receive only surgery. Surgery involves either hysterectomy alone (total or radical) or hysterectomy in combination with bilateral salpingo-oophorectomy, performed as laparotomy or laparoscopy (Miller et al., 2016). Laparoscopic surgery reduces hospital stay (1-2 days compared to 3-7 days in laparotomy) and increases speed of recovery (Martinek et al., 2010). Hysterectomy causes infertility. In pre-menopausal women, oophorectomy leads to menopause accompanied with symptoms, such as atrophic vaginitis, hot flushes, and night sweats. Radiotherapy and/or chemotherapy following surgery are used to treat two thirds of survivors with late stage disease (Stage III & IV). Chemotherapy usually includes a combination of paclitaxel with carboplatin or cisplatin with doxorubicin, and can result in peripheral neuropathy. Of those undergoing radiotherapy, most will receive both external beam (often given 5 days/week for 4-6 weeks) and internal (brachytherapy, usually 1-4

days) treatment (ACS, 2016). Removal of or radiation to lymph nodes may lead to lymphedema that can affect exercise capacity but no research has examined the safety of resistance exercises for reducing lower limb lympoedema risk following endometrial cancer treatment (Schmitz et al., 2010, Audette and Waterman, 2010). Long-term treatment side effects of radiotherapy may include bladder dysfunction, bone damage, which can increase fracture risk, and mild chronic bowel toxicity (Kuku et al., 2013), which can result in diarrhoea and incontinence and, thus, intolerance of high-fibre foods. Atrophic vaginitis and stenosis can lead to impaired sexual function adding to the burden of compromised HRQoL (Schmitz et al., 2010, Audette and Waterman, 2010). Progestins are the main hormone therapy used. Side effects may include night sweats, hot flushes, in addition to increased appetite and fluid retention, both of which that can cause weight gain (ACS, 2016).

Most HRQoL self-reported data comes from mailed surveys, which are prone to non-response biases, under-representation of segments of the population, such as the elderly, those with poorer performance, and the more deprived, and social-desirability biases particularly for surveys that are not anonymous (Groves et al., 2009). In contrast, the data for survivors' physical health (described below) primarily stems from retrospective cohort studies based on medical records review. Conduct of many such studies is in single institutions, which leads to sample selection bias, as the sample might not be representative of the population. Given the general accuracy of the records, recall biases are minimised, particularly if the records are complete. Furthermore, the temporal sequence of risk factors and outcomes is ensured. However, causality cannot be inferred, as with every observational study.

4.1.1 Physical health, well-being, and symptoms

Approximately 10% of endometrial cancer survivors will experience cancer recurrence with tumour grade a significant risk factor for recurrence rate and frequency of distant metastasis (Gayar et al., 2013). On top of this, survivors face a high risk of a second primary cancer, particularly during the first year after diagnosis (Hemminki et al., 2003). The most common include breast, colorectal, ovarian, and small intestine cancers (Hemminki et al., 2003, Curtis et al., 2006). While the reasons remain elusive, DNA damage from radiotherapy and chemotherapy has been postulated as one potential factor. However, a recent analysis of three randomised trials of endometrial and colorectal cancer survivors treated with radiotherapy or only surgery indicated no increased risk of second primary cancer (Wiltink et al., 2015). Despite this, the study demonstrated a significantly higher risk of developing second primary cancer in this cohort compared to the general population. Similar genetic and environmental factors between the two cancers might also play a role. For example, obesity is a shared risk factor among endometrial, colorectal, breast, and ovarian cancers, while physical inactivity is a shared risk factor between endometrial, breast, and colorectal cancers (WCRF, 2013, WCRF, 2007).

Additionally, survivors face significant impairments in their physical well-being. In a survey of 654 UK women with womb cancer, 34% mentioned at least a slight mobility difficulty, with 7% reporting severe difficulty (PHE, 2015). The most frequently reported issue was aches and pains in muscles and joints. More than a third reported dyspnoea and about 40% reported trouble sleeping or being tired. Moreover, lymphoedema was reported by less than 30%. This fluid accumulation results in changes in function and appearance, together with symptoms like pain and numbness, and is associated with reduced physical HRQoL (Rowlands et al., 2014). Another survey of 158 endometrial cancer survivors in the

Netherlands found somewhat lower estimates in the range of 20-30% for fatigue, pain, insomnia, and dyspnoea (Smits et al., 2014). The differences between the two surveys might be explained by the lower percentage of survivors receiving adjuvant treatment in the latter study. A retrospective cohort demonstrated that 32% of those treated with radiotherapy suffer from chronic mild bowel injury symptoms (Kuku et al., 2013).

Nationally representative data in the USA indicate that endometrial cancer survivors have an average of two comorbidities (SD: 1.5) (Blanchard et al., 2008). In a retrospective cohort of 23,277 women with uterine cancer, only 16.4% had no comorbidity with about 26% and 59% having diabetes and hypertension, respectively (Kurnit et al., 2015). Other retrospective chart reviews have indicated equivalent diabetes and hypertension estimates in endometrial cancer survivors (Ko et al., 2014, Nevadunsky et al., 2014). This is in line with the poor physical fitness as measured by peak oxygen consumption in morbidly obese endometrial cancer survivors (mean age 58.3years) compared to matched controls, with 90% of cases scoring below the 10^{th} percentile of age-standardised average values (Modesitt et al., 2012). Furthermore, another retrospective cohort suggested lower bone mineral density and higher osteopenia in 68 endometrial cancer survivors after cancer treatment compared to 225 matched controls, but did not account for any confounding (Oh et al., 2015).

4.1.2 Psychological well-being

In the aforementioned survey of 654 UK women (PHE, 2015), depression or anxiety was the most commonly reported problem. More than a third (37%) of endometrial cancer survivors mentioned at least a slight difficulty and 12% of those reported moderate, severe, or extreme anxiety or depression. In a 2-year prospective cohort, anxiety was significantly reduced from baseline at 3-months and this decrease continued over time, whereas

depression scores remained unchanged (Ferrandina et al., 2014). Interestingly, pain has been positively associated with anxiety, depression, and interleukin-6 in the multivariate analysis of another small prospective cohort post-surgery (Honerlaw et al., 2016). Overlapping neurobiological pathways between depression and pain may account for these associations, such as inflammation and dysfunction of several processes in the central nervous system (Narasimhan and Campbell, 2010).

Distress has also been positively associated with the perceived importance of lifestyle in cancer recurrence prevention among long-term endometrial and cervical cancer survivors who had not made positive dietary changes (Costanzo et al., 2005). On the contrary, this association was negative in those with positive dietary changes after diagnosis.

Furthermore, fear of recurrence is very common in about two thirds of endometrial cancer survivors (PHE, 2015). Indeed, cross-sectional analysis of 2615 survivors of different cancer types, including endometrial cancer, indicated no significant differences in the severity of fear of recurrence between cancer types (van de Wal et al., 2015). The concern, which showed a temporal decline, was positively associated with comorbidity, female gender, and younger age among other factors.

4.1.3 Social well-being and unmet needs

Social function scores are among the highest compared to other HRQoL scales in survey data (Smits et al., 2014, Oldenburg et al., 2013). Nonetheless, a recent survey in 110 endometrial cancer survivors revealed that survivors spontaneously reported a mean 2.74 (SD: 0.94) of unmet needs across 16 different domains (Burg et al., 2015) similar to survivors of other cancer sites. 30%, 24%, 20%, and 19% of these women expressed unmet physical, emotional/mental health, social support, and education/information needs, respectively. Lower prevalence of unmet needs was reported for the rest of the

domains, including personal control, system of care, financial, societal, and provider relationship among others. The low financial unmet needs might be explained due to sampling a high-socio-economic population. The retirement prevalence increases post diagnosis but this might be attributed to either health reasons or expected retirement. Furthermore, 70% of the employed women continue working their usual hours post diagnosis (PHE, 2015). Lastly, a recent narrative review highlighted the mixed evidence regarding sexual dysfunction in this population, with some studies indicating no differences pre and post treatment, between treatments, or compared with matched controls, while others suggesting a lower sexual interest, and libido (Huffman et al., 2016). These differences might partly be explained by the small sample sizes in most studies. In summary, the available evidence suggests that endometrial cancer survivors comprise a high-risk group for both morbidity and mortality.

4.2 Study aim

While the decreased HRQoL that endometrial cancer survivors experience stems primarily from cancer and its treatment (Penson et al., 2006), other factors such as lifestyle behaviours may also play a role. Meeting nutrition and physical activity recommendations is positively associated with HRQoL in cancer survivors (Blanchard et al., 2008). Furthermore, the behavioural interventions presented above demonstrated significant improvements in various health outcomes, including aspects of HRQoL That said, the prevalence of low physical activity, poor dietary quality and obesity is high among endometrial cancer survivors (von Gruenigen et al., 2011). Although endometrial cancer risk is strongly linked with diet, physical activity, and obesity in endometrial cancer risk (WCRF, 2013), data on these factors and outcomes for survivors of endometrial cancer are limited.

4.3 Aims

This review aimed to explore the evidence for an association associations between obesity (BMI, body composition), diet (food groups, dietary patterns), and physical activity with HRQoL in endometrial cancer survivors.

4.4 Methods

4.4.1 Eligibility criteria

Endometrial cancer survivors regardless of the disease stage comprised the population of interest (Pecorelli, 2009, Creasman, 1990). The definition of survivors included those following the end of their primary or adjuvant therapy treatment with or without recurrent disease. Eligible studies were those examining an association (reporting a measure of the effect or association) between obesity, diet, and physical activity with HRQoL in endometrial cancer survivors.

4.4.2 Health-related Quality of Life

HRQoL was conceptually defined earlier in the chapter. The most commonly used and standardised questionnaires to assess HRQoL are the "European Organization for Research and Treatment of Cancer Core Questionnaire" (EORTC QLQ-C30) (Aaronson et al., 1993), the "Functional Assessment for Cancer Therapy-General" (FACT-G) (Cella et al., 1993), and the "Short-Form 36-item Health Survey" (SF-36) (Ware and Sherbourne, 1992). Table 4.1 provides a comparison of their characteristics. Sufficient similarities exist between the physical, emotional, and functional subscales of the EORTC QLQ-C30 and the FACT-G to allow direct comparisons (Holzner et al., 2006). This also holds true for the physical functioning, emotional functioning/mental health and pain subscales between the

EORTC QLQ-C30 and SF-36 (Kuenstner et al., 2002). Strong correlations exist between the FACT-G physical well-being and SF-36 physical composite score as well as between the FACT-G emotional well-being and the SF-36 mental composite score (Ashing-Giwa et al., 2008). Therefore, overall HRQoL, four well-being domains (physical, functional, emotional, and social) and two symptoms (fatigue, and pain) were included in the operational definition of HRQoL.

Table 4.1 Comparison of the characteristics of the three HRQoL measures

		FACT-G		EORTC-QLQ-C30		SF-36	
# items		27		30		36	
Overall structure		4 well-being scales		5 functioning scales and 9 symptom scales		7 functioning & 1 symptom scales clustered in 2 composite scores	
Scaling	Well-being scales	Physical well-being (7)	Functional scales	Physical functioning (5)	Physical Health	Physical functioning (10)	
		Functional well-being (7)		Role functioning (2)		Role physical (4)	
		Emotional well-being (6)		Emotional functioning (4)		Bodily pain (2)	
		Social/family well-being (7)		Social functioning (2)		General Health (5)	
	Symptoms	Fatigue (13)[a]		Cognitive functioning (2)	Mental health	Role emotional (3)	
		Anaemia (7)[a]	Symptom scales/items	Fatigue (3)		Social functioning (2)	
				Pain (2)		Mental Health (5)	
				Nausea & vomiting (2)		Vitality (4)	
				Dyspnoea, Insomnia, Constipation, Diarrhoea, Appetite loss, Financial difficulties (1 each)			
		Overall score (27)		Global health status / QoL (2)			
Item delivery		Statements		Questions		Both questions and statements	
Response options		Likert scales with 5 options		Likert scales with 4 or 7 options		Likert scales with 3, 5 or 6 options Yes/No questions	
Recall period		Past 7 days		Past week		Past 4 weeks	

Parentheses indicate the number of items in each scale.

[a]Added subscales to the FACT-G. Not counted in the overall score of FACT-G but counted in the overall score of FACT-F and/or FACT-An.

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4.4.3 Identification of studies

The initial (published version) search included the following databases from inception until January 2014 with no language restrictions: MEDLINE via PubMed, EMBASE, Cochrane, and PsycINFO (Koutoukidis et al., 2015a). Reference lists from included papers were visually scanned. Furthermore, the websites WHO International Clinical Trials Registry Platform[5], Current Controlled Trials[6], and ClinicalTrials.gov[7] were included in the search. Manual search of relevant conference proceedings and contact with experts for preliminary results of on-going studies were employed to identify unpublished literature. The search protocol was devised with the help of an experienced academic librarian and is available in **Error! Reference source not found.**. In brief, it comprehensively included relevant terms for the exposure (diet, energy balance, body composition, physical activity) and outcome variables (fatigue, pain, HRQoL, physical, psychological, social, and spiritual well-being). An updated PubMed search was conducted in April 2016.

4.4.4 Study selection

Titles and, where available, abstracts were scanned against inclusion criteria. For those that appeared to meet inclusion criteria, full texts were reviewed. Contact to the relevant authors was not sought in the interest of time. Potential ambiguities for study inclusion were discussed with the supervisory team. Duplicate reports of a study were regarded as a single study with reference to all publications. Sample size, authorship, and methodology

[5] www.who.int/ictrp/en

[6] www.controlled-trials.com

[7] www.clinicaltrials.gov

served as identifiers of duplicate publications and the most appropriate data sets were included. When data from the primary papers could not be extracted, secondary analysis of more than one study was included in the analysis.

4.4.5 Data extraction

Microsoft Excel 2011 and EndNote X7 were used for data extraction. Data extraction forms were generated following the guidelines of the Centre for Reviews and Dissemination (CRD, 2009); **Error! Reference source not found.** provides an example form.

4.4.6 Quality assessment

The SIGN checklists were used for methodological quality assessment (SIGN, 2013). Quality of reporting was based on STROBE guidelines for observational studies (von Elm et al., 2007) and the CONSORT statement for clinical trials (Campbell et al., 2004). Table 4.5 presents data on quality assessment for the cohorts and trials.

4.4.7 Data synthesis

As only two randomised controlled trials (RCTs) and one single-arm trial were identified, the data were synthesised narratively (Popay et al., 2006). Outcome measures were used to cluster the studies. To allow comparisons between different measurement tools and sample sizes, standardised mean differences (effect sizes) were produced by calculating Cohen's d = $(Mean_1 – Mean_2)/SD_{pooled}$ between non-obese (i.e. normal weight and overweight) and obese (all categories) and between those meeting guidelines (as defined in the papers) and those who did not. The study of Blanchard et al. (2010) did not mention the number of participants with and without obesity (Blanchard et al., 2010). To allow for inclusion of

these data, the two groups were assumed of equal size in this study. Direction differences were corrected for fatigue and pain scales, so that the same direction was applied to all studies. A small, medium, and large effect size was defined as 0.2, 0.5, and 0.8, respectively (Cohen, 1988).

4.5 Results

The search strategy returned 5057 records. Of those, 17 reports of 12 studies were analysed. The study selection process and reasons for exclusion are presented in the PRISMA flow diagram (Figure 4.1). Five of 12 studies were cross-sectional, two retrospective, two prospective, one single arm trial, and two were randomised-controlled trials. The EORTC-QLQ-C30, the SF-36 and the FACT-G were the most commonly used questionnaires.

Table 4.2 (Blanchard et al., 2008, Courneya et al., 2005, Oldenburg et al., 2013, Smits et al., 2013, Ferrandina et al., 2014, Lin et al., 2014) shows the six studies that assessed overall HRQoL. Four were cross-sectional, one retrospective and one examined baseline data from a prospective longitudinal study. Each of the three aforementioned questionnaires was used in two studies. They demonstrated a similar pattern of higher HRQoL with lower BMI and healthier lifestyle behaviours. In particular, three studies assessed the association between BMI and HRQoL. Three of them found small to medium differences of 0.21 (0.04, 0.37) and 0.29 (0.01, 0.59) and 0.38 (0.10, 0.64) on HRQoL between the non-obese and obese groups (Smits et al., 2013, Oldenburg et al., 2013, Lin et al., 2014) and two found large differences (0.75 (0.54, 0.96) and 1.29 (1.12, 1.46)) (Courneya et al., 2005, Ferrandina et al., 2014). The latter study indicated higher HRQoL with lower BMI and increased physical activity after adjustment for major confounders. Moreover, a large size difference of 0.78 (0.30, 1.26) in HRQoL was observed among survivors meeting the diet (five fruits

and vegetables per day), physical activity, and no smoking guidelines (Blanchard et al., 2008).

Table 4.3 presents the effect sizes for HRQoL domains and symptoms (Basen-Engquist et al., 2009, Blanchard et al., 2008, Blanchard et al., 2010, Courneya et al., 2005, Fader et al., 2011, Oldenburg et al., 2013, Smits et al., 2013, von Gruenigen et al., 2011, Karabuga et al., 2015, Brown et al., 2014, Lin et al., 2014). Better scores for physical well-being were universally demonstrated in the non-obese groups but with large variability ranging from small to large effect sizes. Three (Basen-Engquist et al., 2009, Courneya et al., 2005, Brown et al., 2014) of the five studies found significant medium to large effect sizes for better physical well-being scores in those meeting the physical activity guidelines. In non-obese and physically active survivors, better scores of a small scale or non-significant trends towards them were demonstrated for functional well-being.

Four out of five studies did not indicate an association between emotional well-being and BMI, while one study showed a slightly better score in emotional well-being for non-obese survivors (Smits et al., 2013). Meeting physical activity guidelines was associated with a trend towards better emotional well-being (0.14 (-0.07, 0.36)) (Courneya et al., 2005). The same applied for meeting two of the three health behaviour recommendations compared to those that did not (0.45 (-0.15, 1.05)) (von Gruenigen et al., 2011). However, consistency among studies was lacking (Lin et al., 2014). Social well-being was significantly better (small effect size) among those without obesity in two out of five studies.

Furthermore, neither obesity nor physical activity indicated either a non-significant trend or significant medium-size effects for lower fatigue scores (0.28-0.54). Only one study reported slightly increased fatigue in those without obesity (0.04 (-0.33, 0.41)) (Basen-Engquist et al., 2009). Finally, pain was lower in survivors without obesity. The difference

from those with obesity ranged from -0.11 to -0.47. Furthermore, one study showed a medium size difference (-0.52 (-0.97, -0.07)) in favour of physically active survivors (Basen-Engquist et al., 2009).

The above data on HRQoL domains and symptoms are partly supported by the evidence from clinical trials of lifestyle interventions (Table 4.4) (McCarroll et al., 2013, von Gruenigen et al., 2012, von Gruenigen et al., 2008, von Gruenigen et al., 2009, Basen-Engquist et al., 2014). Only one of the trials, testing a weight loss lifestyle program, demonstrated a significant improvement in physical function at 6 months ($p=0.048$) and reduction in fatigue at 3 months ($p=0.008$) (McCarroll et al., 2013). The single-arm exercise intervention showed significant improvements in physical function and general health both at the end of the intervention and between obese and non-obese groups. However, all trials lacked statistical power to detect differences in HRQoL. Of note, selective reporting and selection bias were evident in the two weight loss lifestyle interventions, given the high prevalence of health behaviours at baseline. None mentioned blinding of the outcome assessor. Their methodological quality was deemed as acceptable (McCarroll et al., 2013) or unacceptable (von Gruenigen et al., 2008, Basen-Engquist et al., 2014).

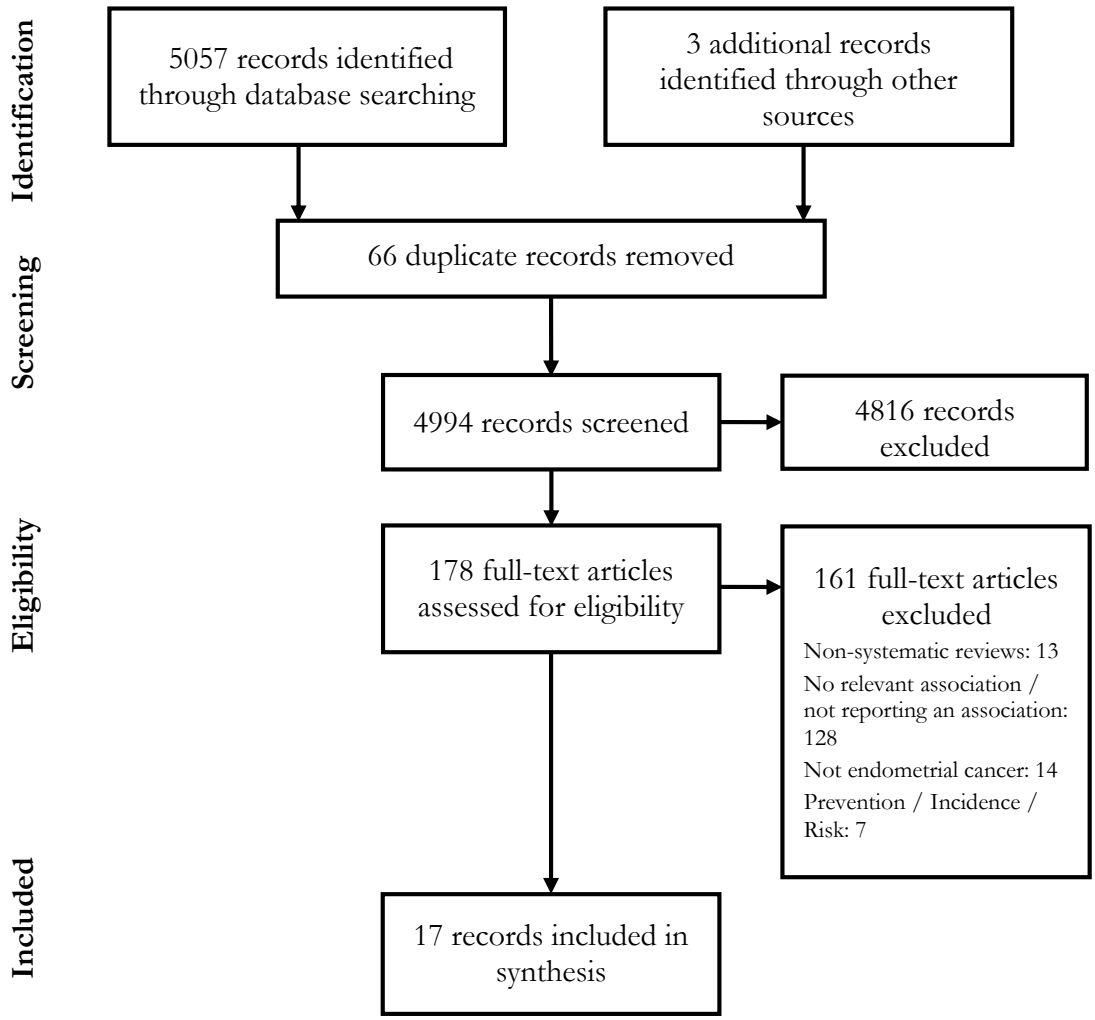


Figure 4.1 PRISMA flow chart of the stages of the literature review

Table 4.2 Effects of exposure variables on HRQoL

Reference	Design	N	BC measure	Diet measure	Physical activity measure	HRQoL Measure	Mean Difference / Coefficient	Covariates included
(Smits et al., 2013)	Retrospective FU: 2.5 years	158	BMI Extracted from medical records	n/a	n/a	EORTC-QLQ-C30	d non-obese vs. obese: 0.29 (0.01, 0.59)	Patient characteristics
(Ferrandina et al, 2014)	Baseline data from prospective longitudinal FUP: 2 years	132	BMI extracted from medical notes	n/a	n/a	EORTC-QLQ-C30	d non-obese vs. obese: 1.29 (1.12, 1.46) No difference over time p=0.081	Univariate model
(Courneya et al., 2005)	Cross-sectional	386	BMI Self-reported weight and height	n/a	Modified Leisure Score Index from Godin Leisure Time Exercise Questionnaire	Total FACT-An	d non-obese vs. obese: 0.75 (0.54, 0.96) BMI on QoL Beta=-0.17, p<0.001 d PA vs. no-PA: 0.48 (0.38, 0.58) Exercise on QoL Beta: 0.21 p<0.001	Age, marital status, education, income, disability, time since diagnosis disease stage, tumour grade, adjuvant therapy
(Oldenburg et al., 2013)	Cross-sectional	666	BMI Self-reported weight and height	n/a	n/a	SF-36	General Health d non-obese vs. obese: 0.21 (0.04, 0.37) BMI on General Health Beta=0.50 (p>0.05)	Age, education, marital status, treatment, time since diagnosis, number of comorbidities
(Blanchard et al., 2008)	Cross-sectional	729	BMI Self-reported weight and height	Self-reported assessed by question: How many days per week do you eat at least 5 servings of FV a day?	Godin Leisure-Time Exercise Questionnaire met/did not met ACS PA recommendation	SF-36	d Meeting PA recommendation vs. not 0.3 Eating 5-a-day vs. not 0.1 PA and 5-a-day and no smoking vs. not 0.78 (0.30, 1.26)	Race, stage, education, marital status, total number of comorbidities
(Lin et al., 2014)	Cross-sectional	213	BMI Self-reported weight and height	n/a	Paffenbarger Physical Activity Questionnaire met/did not met 150min/week	Total FACT-G	d non-obese vs. obese: 0.38 (0.10, 0.64) d physically active vs. not: 0.04 (-0.23, 0.30)	Age, race, pathology, stage, treatment type, number of lymph nodes removed, years since diagnosis, Charlson Comorbidity Index score

BC: Body composition, d: Standardised mean difference. Updated from (Koutoukidis et al, 2015).

Table 4.3 Effect of exposure variables on HRQoL domains and symptoms

Reference	HRQoL measure	Standardised mean difference (95% CI) $d = (Mean_1\text{-}Mean_2) / SD_{pooled}$	
		BMI (non-obese vs. obese)	Physical Activity (met vs. not met guidelines)
		1. Physical well-being	
(Courneya et al., 2005)	FACT-G PWB	0.19 (0.01, 0.40)	0.43 (0.21, 0.65)
(von Gruenigen et al., 2011) [a]	FACT-G PWB	-	0.16 (-0.43, 0.75) [b]
(Fader et al., 2011) [c]	FACT G PWB	0.81 (0.40, 1.23)	-
(Lin et al., 2014) [d]	FACT-G PWB	0.43 (0.16, 0.71)	0.04 (-0.22, 0.31)
(Smits et al., 2013)	EORTC QLQ-C30 PF	0.45 (0.15, 0.74)	-
(Oldenburg et al., 2013)	SF 36 PF	0.76 (0.59, 0.93)	-
(Basen-Engquist et al., 2009)	SF-36 PF	0.66 (0.28, 1.04)	0.86 (0.40, 1.32)
(Blanchard et al., 2010)	SF-36 PHc	0.44 (0.20, 0.69)	-
(Brown et al., 2014) [d]	SF 12 PF	-	1.22 (0.84, 1.59) [e]
		2. Functional well-being	
(Courneya et al., 2005)	FACT-G FWB	0.05 (-0.16, 0.26)	0.26 (0.04, 0.48)
(von Gruenigen et al., 2011) [a]	FACT-G FWB	-	0.35 (-0.25, 0.95) [b]
(Fader et al., 2011) [c]	FACT-G FWB	0.19 (-0.22, 0.60)	-
(Lin et al., 2014)	FACT-G FWB	0.35 (0.08, 0.62)	0.01 (-0.26, 0.28)
(Smits et al. (2013)	EORTC QLQ-C30 RF	0.31 (0.01, 0.60)	-
(Karabuga et al., 2015)	EORTC QLQ-C30 RF	* [f]	-
		3. Emotional well-being / mental health	
(Courneya et al., 2005)	FACT-G EWB	0.06 (-0.14, 0.27)	0.14 (-0.07, 0.36)
(von Gruenigen et al., 2011) [a]	FACT-G EWB	-	0.45 (-0.15, 1.05) [b]
(Fader et al., 2011) [c]	FACT-G EWB	0.12 (-0.28, 0.53)	-
(Lin et al., 2014)	FACT-G EWB	-0.07 (-0.34, 0.20)	0.03 (-0.24, 0.30)
(Smits et al., 2013)	EORTC QLQ-C30 EF	0.25 (0.09, 0.42)	-
(Oldenburg et al., 2013)	SF -36 MHs	0.12 (-0.04, 0.29)	-
(Blanchard et al., 2010)	SF -36 MHc	0.16 (-0.09, 0.40)	-
		4. Social well-being	
(Courneya et al., 2005)	FACT-G SWB	0.20 (-0.01, 0.41)	0.33 (0.23, 0.33)
(Fader et al., 2011) [c]	FACT-G SWB	0.30 (0.14, 0.46)	-
(Lin et al., 2014)	FACT-G SWB	0.16 (-0.10, 0.44)	0.03 (-0.24, 0.30)
(Oldenburg et al., 2013)	SF-36 SF	0.12 (0.05, 0.20)	-
(Smits et al., 2013)	EORTC QLQ-C30 SF	0.25 (-0.05, 0.54)	-
		5. Fatigue	
(Courneya et al., 2005)	FACT-F	-0.42 (-0.62, -0.21)	-0.40 (-0.61, -0.18)
(von Gruenigen et al., 2011) [a]	FACT-F	-	-0.54 (-1.14, 0.06) [b]
(Smits et al., 2013)	EORTC QLQ-C30 F	-0.28 (-0.58, 0.01)	-
(Oldenburg et al., 2013)	FAS	-0.34 (-0.50, -0.17)	-
(Basen-Engquist et al., 2009)	BFI	0.04 (-0.33, 0.41)	-0.44 (-0.89, 0.01)
		6. Pain	
(Basen-Engquist et al., 2009)	BPI	-0.11 (-0.48, 0.26)	-0.52 (-0.97, -0.07)
(Smits et al., 2013)	EORTC QLQ-C30 P	-0.30 (-0.59, -0.01)	-
(Oldenburg et al., 2013)	SF-36 BP	-0.47 (-0.64, 0.31)	-

[a] Secondary analysis of McCarroll et al. (2013), (von Gruenigen et al., 2008).
[b] Meeting either 5-a-day and no smoking or 150min/week and no smoking.
[c] Secondary analysis of McCarroll et al. (2013), (von Gruenigen et al., 2008),
[d] Data from the same population.
[e] Effect size based on comparison between participants with 3-5.9h/wk and <1h/wk moderate PA.
[f] Effect size could not be calculated but role functioning was higher in the normal weight group (p=0.019).
PWB: Physical well-being, PF: Physical function, PHo: Physical composite score, FWB: Functional well-being, RF: Role-functional, EWB: Emotional well-being, EF: Emotional functioning, MHs: Mental health composite score, SWB: Social well-being, SF: Social functioning, F: Fatigue, FAS: Fatigue Assessment Survey, BFI: Brief fatigue inventory, BPI: Brief Pain Inventory, P: Pain, BP: Bodily pain
Updated version of the table from (Koutoukidis et al., 2015)

Table 4.4 HRQoL after lifestyle interventions

Reference	Study characteristics	Total N	Body composition Measure		Diet measure		Physical activity measure		HRQoL Measure	Mean Difference Between Groups at 6m/12m/Coefficient	Covariates included
(von Gruenigen et al., 2008) (von Gruenigen et al., 2009)	RCT Stage I / II endometrial cancer Lifestyle intervention for 6months vs. usual care FU: 12 months Type I EC: 100%	45 ITT Response rate: 40% Attrition rate: 16% Completion rate: 80% Adherence: 73%	BMI measured		3-day dietary records (1 weekend, 2 weekdays) at 3, 6 & 12 months		4-item Leisure score index from Godin leisure time exercise questionnaire Classified as mild – moderate – strenuous		FACT-F HRQoL Physical WB Functional WB Emotional WB Social WB Fatigue SF-36	Effect size at 12m (LI - UC) -0.14 (-0.61, 0.33) -0.10 (-0.57, 0.38) -0.13 (-0.61, 0.35) -0.29 (-0.77, 0.18) 0.10 (-0.38, 0.57) -0.15 (-0.62, 0.32) Not reported	Baseline
				Effect size at 12m (LI - UC)		Effect size at 12m (LI - UC)		Effect size at 12m (LI - UC)			
			BMI	-0.5 kg/m²	Total Intake	-90kcal	LSI	15.8**			
			Weight	-4.9 kg *	Vit C Intake	15.6 mg	Pedometer	Not reported			
					Folate Intake	101.4 mcg					
(McCarroll et al., 2013) (von Gruenigen et al., 2012)	RCT Stage I / II endometrial cancer Lifestyle intervention for 6months vs. usual care FU: 12 months Type I EC: 100%	75 ITT Response rate: 19% Attrition rate: 21% Completion rate: 78% Adherence: 84%	BMI measured Body composition using DXA (not reported) Biomarkers (not reported)		Two 24h recalls Classified as F&V servings/day Classified as kcal/day		4-item Leisure score index from Godin leisure time exercise questionnaire and duration questions 7-day pedometer step test at baseline and 6 months		FACT-G (assessed at baseline and 3, 6, and 12 months)	Fatigue at 3 months significantly different between groups p=0.008 Physical function at 6 months significantly different between groups p=0.048 The total FACT-G score was improved in the LI group from baseline to 3 months (p<0.05) and 6 months (p<0.001)	Age, time since diagnosis, stage, adjuvant treatment, co-morbidities and baseline
				Effect size at 12m (LI - UC)		Effect size at 12m (LI - UC)		Effect size at 12m (LI - UC)			
			BMI	-1.8 kg/m²	Total Intake	-187 kcal ***	LSI	7.8 points ***			
			Weight	-4.6 kg ***	F&V	0.9 servings/d ***	PA Mins	89min/wk ***			
			Waist Circum	-1.6 cm *			Pedometer	Not measured at 12m			

Reference	Study characteristics	Total N	Body composition Measure	Diet measure	Physical activity measure	HRQoL Measure	Mean Difference Between Groups at 6m/12m/Coefficient	Covariates included
(Basen-Engquist et al., 2014)	Single arm intervention Stage I-IIIa endometrial cancer Home-based exercise (walking) with telephone counselling for 6months FUP: 6 months Type I EC: NA	100 Response rate: 16% Attrition rate: 21% Completion rate: 68% Adherence rate: 40%	BMI measured Waist circumference measured Effect size N/A	Not measured	Accelerometer and self-report diaries Effect size N/A	SF-36 (assessed at baseline and 6 months) QLACS BSI-18 Perceived stress scale	SF-36: Significant improvements over time in physical functioning, perceived general health, mental health, and vitality. QLACS: Significant improvements over time in the positive and negative feelings, cognitive problems, pain, sexual problems, fatigue, social avoidance, perceived benefits, and recurrence distress. Perceived stress: Significant improvements over time. No significant group × time interactions.	Age, education, race, time since diagnosis, disease stage, treatment type
			Effect size N/A BMI changes at 6months (not reported) Waist circum. Non-significant changes over time in obese and in non-obese participants		Significant improvements over time in exercise minutes	SF-36 General health Physical function Pain Role physical Vitality Social function Role emotional Mental health	d non-obese – obese at 6m 0.70 (0.28, 1.12) 0.89 (0.46, 1.31) 0.48 (0.07, 0.90) 0.23 (-0.17, 0.64) 0.29 (-0.12, 0.70) 0.25 (-0.16, 0.66) 0.16 (-0.25, 0.57) 0.05 (-0.36, 0.46)	

FU: Follow-up, ITT: Intention-to-treat analysis, LI: Lifestyle Intervention, US: Usual Care, DXA: Dual energy x-ray absorptiometry, F&V: Fruits & Vegetables, LSI: Leisure Score Index
*p<0.05 Significant compared to baseline, **p<0.05 between groups, ***p<0.001 between groups

Table 4.5 Methodological quality in cohorts and clinical trials with HRQoL outcomes

		Cohorts		Trials		
	SIGN Methodological Quality (Yes=1, No=0, Can't say=3) High quality (++) Acceptable (+) Unacceptable (-)	Smits et al. (2013)	Fader et al. (2011)	Von Gruenigen et al. (2008, 2009)	McCarroll et al. (2013), Von Gruenigen et al. (2012)	Basen-Engquist et al., (2014)
2.1	How well was the study done to minimise the risk of bias or confounding?	-	+	-	+	-
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	0	0	0	0	0
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	1	1	1	1	1

4.6 Discussion

HRQoL was negatively associated with both not meeting the healthy lifestyle guidelines and obesity in endometrial cancer survivors. Stronger associations were observed for physical well-being and fatigue. The effect sizes were limited and with wide standard deviations. However, their magnitude was similar to those in the general population (Ul-Haq et al., 2013) and in survivors of breast, prostate and colorectal cancer (Blanchard et al., 2008, Schlesinger et al., 2014, George et al., 2014). This suggests that a healthy lifestyle (healthy diet and weight, physical activity, and no smoking) is associated with better HRQoL in this population. Inference of causality is not possible, given the cross-sectional design of most studies.

The presented data were in agreement with a meta-analysis in cancer survivors demonstrating higher HRQoL after exercise interventions (Mishra et al., 2012). Although the potential for cancer survivors to attain desirable and recommended levels of physical activity might be improbable, physical activity trials have demonstrated improvements in aerobic capacity (Bourke et al., 2014); a firm mortality predictor (Jones et al., 2012). Facilitating physical activity among endometrial cancer survivors is imperative, due to their poor physical fitness levels (Modesitt et al., 2012, Peel et al., 2015) and the potential for substantial health benefits through small behaviour changes (Warburton et al., 2006). Furthermore, physical activity seems to ameliorate cancer-related fatigue (Cramp and Byron-Daniel, 2012). However, fatigue mechanisms remain unclear. Further studies can provide insight on the postulated dysfunctions of the central nervous system rather than abnormal muscle metabolism (as in malnutrition-related fatigue) that drive cancer-related fatigue (Kisiel-Sajewicz et al., 2013).

Unfortunately, dose-response relationships could not be established. However, many studies (Blanchard et al., 2008, Courneya et al., 2005, Oldenburg et al., 2013, Smits et al., 2013) pointed towards this being the case, given the positive association between healthy lifestyle and aspects of HRQoL, which seems consistent with results in survivors of different cancers (Blanchard et al., 2008). The links of body composition and diet with HRQoL remain unclear in this population, despite the fact that central adiposity predicts mortality stronger than BMI in women (Taylor et al., 2010). Thus, future reporting of the pre-specified body composition and serum biomarkers measurements in one of the trials (McCarroll et al., 2013) may further elucidate the intervention effects on the nutritional status of this population.

Weight loss is an attractive endpoint in cancer survivorship research. While unintentional weight loss is a strong predictor of prognosis (Bamia et al., 2010) there is a lack of substantial evidence on the effects of intentional weight loss in this population. Nonetheless, the largest trials in other cancer survivors and the overall literature on obese older adults can provide valid insights. Indeed, they strongly support that HRQoL - especially physical function – and cardio-metabolic risk factors with minor side effects can improve in obese elderly adults following a lifestyle intervention that involves weight loss (Felix and West, 2013, Villareal et al., 2011, Bouchonville et al., 2014). However, improvements were significantly greater in both physical function and cardio-metabolic risk factors when weight loss was accompanied by exercise training (flexibility, aerobic, resistance, and balance training) (Villareal et al., 2011, Bouchonville et al., 2014). In this trial, muscle and bone mass decreased; expected consequences of weight loss. However, the diet-exercise group had higher preservation of lean and bone mass compared to exercise only, diet only, or control group (Villareal et al., 2011). The potential mechanisms have been previously discussed (Waters et al., 2013b).

A one-year home-based, weight loss, diet-exercise intervention demonstrated significant improvements in physical function of colorectal, breast, and prostate cancer survivors (Demark-Wahnefried et al., 2012). Of note, intervention adherence was strongly correlated with HRQoL outcomes (Winger et al., 2014) with intervention cessation to reduce the beneficial effects (Demark-Wahnefried et al., 2012, Waters et al., 2013a). Similar results were observed in the largest most-intensive behavioural weight loss intervention in breast cancer survivors, in which physical function and vitality were significantly improved at 6 months but did not differ between arms at 2 years (Demark-Wahnefried et al., 2015).

While these trials did not assess body composition, the value of weight loss in this setting is highly debatable given the unavoidable loss of lean mass, as this can increase risk of sarcopenia and eventually worsen outcomes (Martin et al., 2013). Thus, loss of fat mass with preservation of muscle mass seems a prudent option for older obese adults and cancer survivors. For this goal, resistance exercise and a plant-based protein-rich diet remain the two main strategies. Both mathematical modelling[8] and case series in older male cyclists suggest this would require an extreme (and sustained) change in physical activity levels (Hall et al., 2011, Rosenkilde et al., 2015). This would be highly unlikely to be achieved by the majority of endometrial cancer survivors in real-world settings. Furthermore, the long-term resistance to intentional weight change (especially weight loss) due to physiological mechanisms should also be acknowledged. These feedback loops remain largely unclear

[8] Example case: A 65-year old sedentary (PAL: 1.5) woman with a BMI of 36.7kg/m^2 (weight: 100kg) would require to add 40 minutes 5 times per week of each of swimming, medium cycling, and intense walking in order to achieve a 5% weight loss in 6 months and maintain her muscle mass. This reflects a 158% change in her current physical activity levels. Based on the USDA body weight planner (www.supertracker.usda.gov).

(Muller et al., 2014) but encompass pre-occupation with palatable food, increased hunger, and reduced satiety and energy expenditure (Leibel et al., 1995, Sumithran et al., 2011, Stice et al., 2013) through changes in hormones and the nervous system. A secondary analysis of the PREDIMED trial also suggested the relative significance of adherence to a high-quality diet over weight loss for cardiovascular disease prevention (Estruch et al., 2016). Perhaps, efforts should, initially, be focused on achieving and maintaining all the healthy lifestyle recommendations and, for those able to achieve those, on weight loss, and substantially high levels of physical activity.

Since the submission for publication of the initial version of this review (Koutoukidis et al., 2015a), one meta-analysis examined the association of BMI and HRQoL in endometrial cancer survivors. Another one examined the effect of the lifestyle interventions on HRQoL in endometrial and ovarian cancer survivors. Both yielded similar conclusions to the current results, such as an inverse association between obesity and HRQoL and a lack of high-quality evidence in lifestyle interventions (Smits et al., 2015a, Smits et al., 2015b). From a methodological perspective, meta-analysing results of cross-sectional studies might produce spurious results given the high risk of bias and confounding (Egger et al., 2001). The meta-analysis of the lifestyle interventions was able to include only two of the three RCTs in the final model indicating the poor quality of reporting in the literature.

The current review was conducted following the PRISMA guidelines (Moher et al., 2009) but given the scoping nature of the review, intervention and comparison criteria had not been pre-specified. A comprehensive search strategy was employed. Adherence to the quality of reporting guidelines in future studies should be further promoted. Only the single-arm trial reported objectively measured physical activity, which should be encouraged in future studies. Most studies used self-reported, validated questionnaires, which are prone to recall and social desirability bias.

Further strengths include the acceptable convergent validity of most scales of HRQoL measures that allows direct comparisons, despite that the EORTC QLQ-C30 and SF-36 are functional assessments whereas the FACT-G measures well-being. The non-significant results in social well-being in the current study but significant when meta-analysed (Smits et al., 2015a) are not very informative, mainly due to significant differences in this scale between the various instruments (Luckett et al., 2011). Where possible, effect sizes were calculated to eliminate instrument-specific effects. Another point is that the observed differences are based on subjective assessments and, therefore, rely on the individual's perceptions of the level of each scale they experience, which may vary among individuals (Osoba et al., 1998). Of note, the presented effect sizes indicate statistical significance, but associate well with clinical significance (Osoba et al., 1998). Therefore, one can cautiously translate the medium-size differences in overall HRQoL, physical well-being, and fatigue to clinically important differences, targeting optimal intervention design. Finally, generalising the results to this group who are often of low socio-economic level (NCIN, 2013) is difficult given the lack of reporting of socio-demographic data in some studies, and high education level and lack of ethnic diversity in others.

4.6.1 Implications for practice and research

Longitudinal studies on the effect of weight control, physical activity, and diet in this population and their association with HRQoL could provide further insights. Potential late-treatment effects, such as fatigue, lymphoedema, or neuropathy, may compromise ability and motivation for physical activity engagement and require further study. Furthermore, late-treatment effects, such as bowel-obstruction, may compromise the range of dietary choices, particularly the high-fibre varieties that offer significant cardio-metabolic protection. Given the lack of dietary data, future studies should address dietary quality,

groups, and patterns in this population. This will help in tailoring behaviour change interventions for this population, so that they might be more efficacious.

Moreover, generalisability of the findings will be improved by recruiting representative samples of cancer survivors in intervention trials, but behaviour change can be challenging. Reasons include socio-economic and environmental constraints (Blaney et al., 2013), coupled with cancer-related effects, limited social support, lack of motivation, and uncertainty about the effects of diet (Blaney et al., 2013, Hefferon et al., 2013, Maley et al., 2013). Behaviour change techniques that foster physical activity include self-monitoring, social support, practice and rewards (Olander et al., 2013). In contrast, effective techniques for dietary change are less clear, due to inaccurate reporting in most trials (Avery et al., 2013). These are further discussed in Chapter 7. Self-efficacy regarding weight management improved following lifestyle intervention in early-stage endometrial (McCarroll et al., 2013), and other cancer survivors (Mosher et al., 2013). Further weight loss and exercise trials with HRQoL outcomes are expected to report in the following years (Hawkes et al., 2014b, Nock et al., 2014, Smits et al., 2015c).

Despite limited data, it is reasonable to speculate that sarcopenia, and even cachexia, might be prevalent (Laky et al., 2010). These conditions add significantly to the mortality burden of obesity (Kalyani et al., 2014). Thus, expansion of the research agenda to other nutrition indices such as waist-to-height ratio, handgrip strength, and body composition in conjunction with BMI could provide a better understanding of the needs of this population.

4.6.2 Conclusions

The data, while predominantly cross-sectional, indicate that overall HRQoL and physical well-being are positively correlated with meeting lifestyle recommendations, while fatigue is

negatively associated with meeting them. There is a need for further research on the health behaviours of this population and how best to inform behaviour change programs. This is addressed in Chapter 5 and Chapter 6. Until solid conclusions can be drawn, health care professionals and policy makers should work towards facilitating the implementation of the existing nutrition and physical activity recommendations (Rock et al., 2012) in cancer survivors. Behavioural lifestyle interventions to improve the suboptimal health behaviours may lead to improvements in HRQoL and should be further evaluated through randomised controlled trials (Chapter 8).

Chapter 5 Diet, nutrition, and physical activity of endometrial cancer survivors: an exploratory cross-sectional study

5.1 Introduction

The studies reviewed in the two previous chapters have defined obesity through body mass index. The international acceptability of BMI lies in its low-cost, convenience, and good correlation with adiposity and established J-shape relationship with chronic diseases. However, BMI does not differentiate between fat and fat free mass (Blundell et al., 2014); both being independent prognostic factors in cancer populations. The challenge in cancer populations is cancer cachexia; a syndrome characterised by loss of muscle mass that is not fully reversible by conventional nutritional support and leads to functional impairment (Fearon et al., 2011). Although cachexia might be clinically obvious in many cases, obesity may mask the cachexia-associated muscle loss; a condition termed "sarcopenic obesity". This condition leads to the poorest prognosis when compared with sarcopenia alone, obesity alone, or normal body composition (Martin et al., 2014). Therefore, simple and

inexpensive ways of measuring body composition, such as bioelectrical impedance, may be useful clinical assessment tools. Unlike other cancer sites, literature sparsely reports the body composition of endometrial cancer survivors. A previous small cross-sectional study indicated no differences in fat mass or fat free mass among endometrial cancer survivors and controls (Modesitt et al., 2012). However, a recent review recommended depletion of muscle mass be assessed using an indirect or direct measure of fat free mass normalised for height combined with fat mass (Bosy-Westphal and Muller, 2015).

These data could inform intervention development if supplemented with data on health behaviours and health beliefs that have been currently scarce based on the findings presented in the previous chapters. Relevant health belief concepts include worry, cancer recurrence attributions (Costanzo et al., 2005), risk perception (Dillard et al., 2012), and social support (Barber, 2013).

5.2 Aims

Thus, the aim of the current study was to examine the nutritional status, health behaviours, and health beliefs of endometrial cancer survivors. The study also aimed to provide first-hand indications about the recruitment challenges in the clinic environment and allow sufficient time to address them for the trial. Finally, it aimed to pilot the instruments to be used in the study assessments and allow for refinement if needed.

5.3 Methods

5.3.1 Study design and participants

Participants for this cross-sectional study were recruited from the outpatient clinics at the University College London NHS Foundation Trust Hospital Gynaecological Cancer

Centre. Recruitment began in June 2014 and terminated in February 2015. A member of the clinical team identified potential participants from the clinic lists. These patients were considered for participation by the member of the clinical team primarily responsible for their care i.e. their consultant or nurse specialist. Participants consented for the study through standard procedures to the researchers attending the clinic (DAK or AL). An MSc student, Xiao Ni, also attended the clinic in summer 2014.

Adult women with sufficient command of English were eligible if they had been primarily diagnosed with histologically confirmed endometrioid adenocarcinoma of endometrial cancer (type I), and were within one year out of any active treatment. In this study, women diagnosed with type II endometrial cancer (clear cell, clear cell or papillary serous carcinomas and sarcomas) were excluded given the differences in morphology and prognosis (Felix et al., 2010), as the aim was to study a more homogenous population. Diagnosis of a secondary cancer, childhood cancer, being more than one year out of any active treatment, and lack of capacity to participate in the study session were also exclusion criteria. The study aimed to recruit 25 early (I/II) and 25 late (III/IV) stage endometrial cancer survivors. Approval to conduct the study has been granted by the NHS Research Ethics Committee (Reference: 14/EE/0113).

A one-to-one 90-minute appointment with the researcher (DAK) was arranged at the Institute of Sport, Exercise, and Health at a time convenient to the participant. The questionnaire is available in **Error! Reference source not found.**.

5.3.2 Measures

5.3.2.1 Dietary intake

Dietary intake was estimated by a single 24-hour weekday recall interview using the Automated Self-Administered 24-hour dietary recall (ASA24) software. This is a free, user-friendly, web-based platform developed by the National Cancer Institute, USA. Participants report their intake with the assistance of the researcher. The tool has shown acceptable validity with 80% of the items truly consumed to be reported (Kirkpatrick et al., 2014). It has also been used in trials with cancer survivors (Rock et al., 2013). Recorded foods have been transferred to the DINO dietary assessment software (MRC Human Nutrition Research Unit, University of Cambridge) (Fitt et al., 2015) that incorporates a British food database, given the country-specific food nutritional composition (Uusitalo et al., 2011). The Alternative healthy eating index 2010 (AHEI-2010), which scores participants' diet against the recommended healthy eating patterns was calculated (Akbaraly et al., 2011). Although this method does not account for the day-to-day variations in dietary intake and, thus, does not provide objective capture of individual's intake, it provides an initial proxy of dietary intake in this group. Moreover, the study provided an indication if ASA24 is a fit-for-purpose measure for this population and this study setting. An updated version of the DINE food frequency questionnaire (Roe et al., 1994) was also used together with questions about alcohol, fruits, and vegetables to assess agreement between the two methods and inform choice of measure for intervention design.

5.3.2.2 Eating behaviour

The Weight Efficacy Lifestyle (WEL) Questionnaire (Clark et al., 1991) is a validated 20-item measure in which participants rate their confidence in resisting eating in response to

five situational factors (negative emotions, availability, social pressure, physical discomfort, and positive activities). It has been previously used in a lifestyle intervention of endometrial cancer survivors showing acceptable responsiveness (McCarroll et al., 2013). Moreover, the ten-item Shape-Up evaluation questionnaire (Chadwivk and Miller, 2014) was used to assess how participants' behaviours currently reflect the Shape-Up components.

5.3.2.3 Physical activity

Physical activity was assessed using the Stanford seven-day physical activity recall, an interview-driven questionnaire (Sallis et al., 1985). The tool reduces recall bias for the light activities that are generally substantial. It shows acceptable reliability and validity against double-labelled water, the gold-standard method, in elderly men (Bonnefoy et al., 2001). It is designed to be responsive to change and can be administered in about 15 minutes. Exercise preferences are measured with a questionnaire previously used with endometrial cancer survivors (Karvinen et al., 2006).

5.3.2.4 Anthropometry and body composition

Height was measured to the nearest 0.1cm using a stadiometer with the participant placing their head in the Frankfurt horizontal plane position. Weight was measured using the body composition analyser to the nearest 0.1kg. Both were measured with bare feet and with light clothing. Body mass index (BMI) was estimated based on the WHO criteria (WHO, 2015). Body composition was determined using the TANITA MC980 multi-frequency segmental body composition analyser using a standardised protocol (Tanita, 2013). Body composition was automatically calculated from an algorithm developed by the manufacturer. Fat mass index (FMI) and fat free mass index (FFMI) were calculated based on the BMI formula using the following equations:

$$FMI = FM\ (kg) \div height\ (m)^2 \quad (1)$$

$$FFMI = FFM\ (kg)\ \div height\ (m)^2 \quad (2)$$

Previously suggested cut-offs were used to estimate low, average, high, and very high FMI and FFMI (Kyle et al., 2005). BMI, %fat, FFMI, FMI, and age were plotted together in a five-dimensional plot similar to Hattori charts for a closer examination of body composition (Hattori et al., 1997). Participants reported their current weight and their weight three and six months ago. This retrospective examination based on the Subjective Global Assessment (Detsky et al., 1987), the most-commonly used measure of malnutrition assessment in cancer patients (Sealy et al., 2014), aimed to identify potential weight changes. Furthermore, participants were asked to describe their weight as very underweight, slightly underweight, about the right weight, slightly overweight, very overweight and if they are trying to get or lose weight or neither of those.

5.3.2.5 Worry

Worry about health was assessed using a single question: "How often have you worried about your overall health in the past year?" with five response options (1=not at all to 5=all the time) (Ferrer et al., 2013). Worry about health has demonstrated complex correlations with eating patterns (Ferrer et al., 2013). Behaviour change due to worry about health was assessed with two items "How much has worrying about your health led you to change the way you ate / to be more physically active in the past year?" with four response options Not at all, a little somewhat, quite a bit, all the time.

5.3.2.6 Cancer recurrence attributions

Participants were asked to rate the importance of various factors causing cancer recurrence on a five-point scale (not at all important to very important). Factors were based on a previous study with endometrial cancer survivors (Costanzo et al., 2005).

5.3.2.7 Risk perception

Perception of risk of recurrence and perception of risk for developing a second cancer were evaluated with three different measures (Dillard et al., 2012). First, participants were asked to respond to four feeling-of-risk questions "If I never change my diet / physical activity habits, I would feel very vulnerable to getting womb cancer again / another type of cancer" with an absolute 7-point scale (strongly disagree to strongly agree). Secondly, the two measures "Compared to an average person of my sex and age, my chances of getting womb cancer / any other cancer are…" evaluated comparative risk perception with a 7-point response scale (Much low to Much higher). Lastly, participants were asked to respond to the statement "If I never change my diet / physical activity habits, I think my chances of getting womb cancer again / any other cancer would be…" with an absolute 7-point verbal scale (Almost zero, very small, small, moderate, large, very large, almost certain).

5.3.2.8 Social support

Social support for physical activity and healthy eating were assessed with a brief set of questions. This theory-based measure has demonstrated adequate reliability and validity (Carlson et al., 2012). The same set of questions was adapted to measure social support for physical activity.

5.3.2.9 Health-related Quality of life

HRQoL was measured with the reliable and validated EORTC QLQ-C30 and QLQ-EN24 measures (Aaronson et al., 1993, Greimel et al., 2011).

5.3.2.10 Statistical analysis

Continuous variables were reported by descriptive statistics (non-missing sample size, mean, standard deviation, median, maximum and minimum). Categorical variables were summarised using frequencies and percentages. Spearman's rank correlation coefficient examined the associations between the risk perception measures and Cronbach's alpha the internal reliability of the WEL questionnaire. Statistical significance was set at $p=0.05$. The level of agreement in reporting of fruit and vegetable intake between the FFQ and the 24-h recall was estimated using the Bland-Altman analysis. Given the limited sample size, no further analysis was performed due to the inherent interpretation challenges. The measures 5.3.2.2 , 5.3.2.5 , 5.3.2.6 , 5.3.2.7 , 5.3.2.8 , and 5.3.2.9 were added to the study after five participants had completed their assessments. For those participants, missing data were ignored and the analysis is presented for 21 participants. The Statistical Package for Social Sciences (SPSS, Chicago, IL) version 22 was used for the whole data analysis. The Hattori-style chart was created using the KNIME Analytics Platform, version 2.11.2.

5.4 Results

Table 5.1 shows the demographic characteristics of the 26 participants. The majority were married, retired, and White.

Table 5.1 Sample demographic characteristics (N=26)

Age	66 ± 12.4
Employment	
Retired	61.5%
Part-time	15.4%
Other	23.1%
Education	
Degree or higher	26.9%
No formal qualifications	26.9%
In between	46.2%
Marital status	
Married	61.5%
Widowed	15.4%
Divorced	15.4%
Single	7.7%
Race	
White	84.6%
Asian	11.4%
Black	3.8%

5.4.1 Dietary intake

Dietary recall through the ASA24 software was feasible and acceptable by participants with each recall to last about 30 minutes. However, proxies for some foods commonly consumed in the UK (e.g. marmite, nut roast) were entered in the software. With an ideal AHEI-2010 score of 110, participants scored a median of 58.88 (IQR: 50.24 – 68.03). Figure 5.2 shows the scores for each component of the dietary index, indicating suboptimal consumption of vegetables, fruits, whole grains, and nuts but optimal consumption (i.e. low quantities) of sugar-sweetened beverages, red and processed meat, and *trans* fats. Based on both the FFQ and 24-h recall, 28% of participants reported meeting the 5-a-day guideline. On average, the intake based on FFQ was 0.93 servings/day higher compared to

the 24-hour recall but the 95% limits of agreement between the two measures ranged from -5.1 to 3.2 (Figure 5.1). This indicated a high level of disagreement between the two measures. Furthermore, only 14% of participants reported increasing their fruit and vegetable intake after their cancer diagnosis with the majority (76%) reporting no changes and 10% stating they ate less fruit and vegetables.

5.4.2 Eating behaviour and Shape-Up questionnaire

On average, participants scored highly on all subscales of the WEL questionnaire indicating high efficacy in dealing with external and internal triggers to unhealthy eating behaviours (Table 5.2 & Figure 5.3). All scales indicated high internal consistency, as shown by the respective Cronbach's alphas. The ceiling effects were considerable, as more than 15% of participants achieved the highest possible score for each question. However, some participants particularly struggled to understand some of the questions and the interviewer had to explain the questions in detail. Furthermore, they generally agreed or strongly agreed with all but one (weight satisfaction) components of the Shape-Up questionnaire (Figure 5.4).

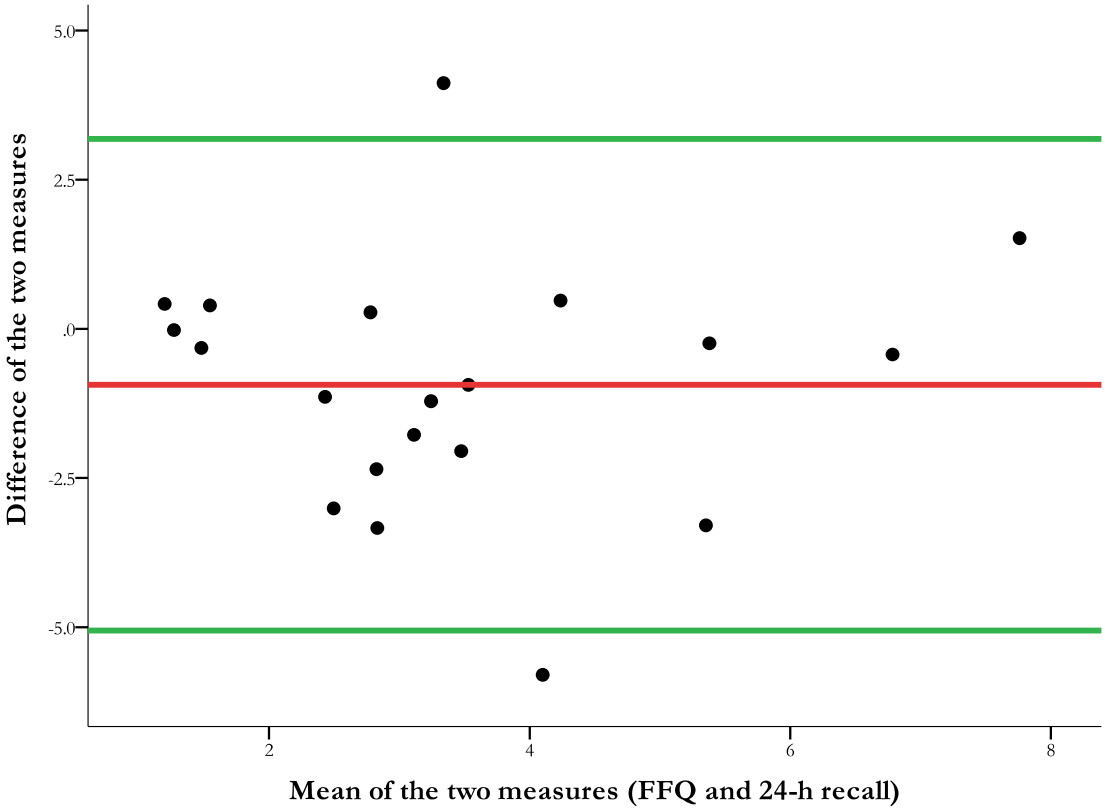


Figure 5.1 Mean bias ±2 SD in reporting servings of fruit and vegetables between FFQ and the 24-h dietary recall

Table 5.2 WEL questionnaire subscale scores (n=21) IQR: Interquartile range

	Median (IQR)	Range	Highest possible score	Cronbach's alpha
Total score	138.0 (119.0 - 166.0)	81.0 - 180.0	180.0	n/a
Negative emotions score	28.0 (21.0 - 36.0)	5.0 - 36.0	36.0	0.87
Availability score	26.5 (22.0 - 30.0)	14.0 - 36.0	36.0	0.84
Social pressure score	30.0 (23.0 - 35.0)	13.0 - 36.0	36.0	0.92
Physical discomfort score	33.0 (27.0 - 36.0)	20.0 - 36.0	36.0	0.85
Positive activities score	29.5 (24.0 - 34.0)	8.0 - 36.0	36.0	0.83

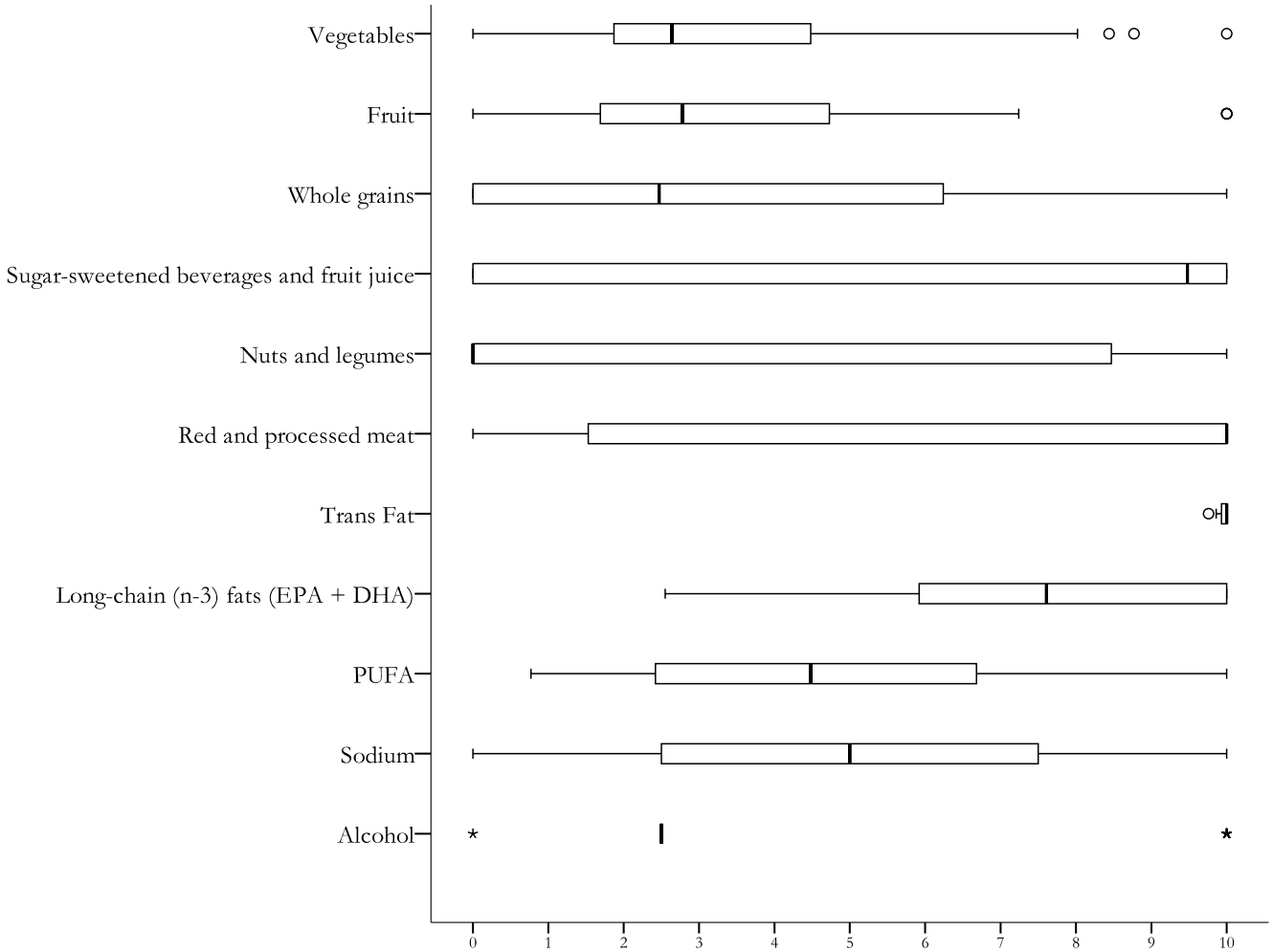
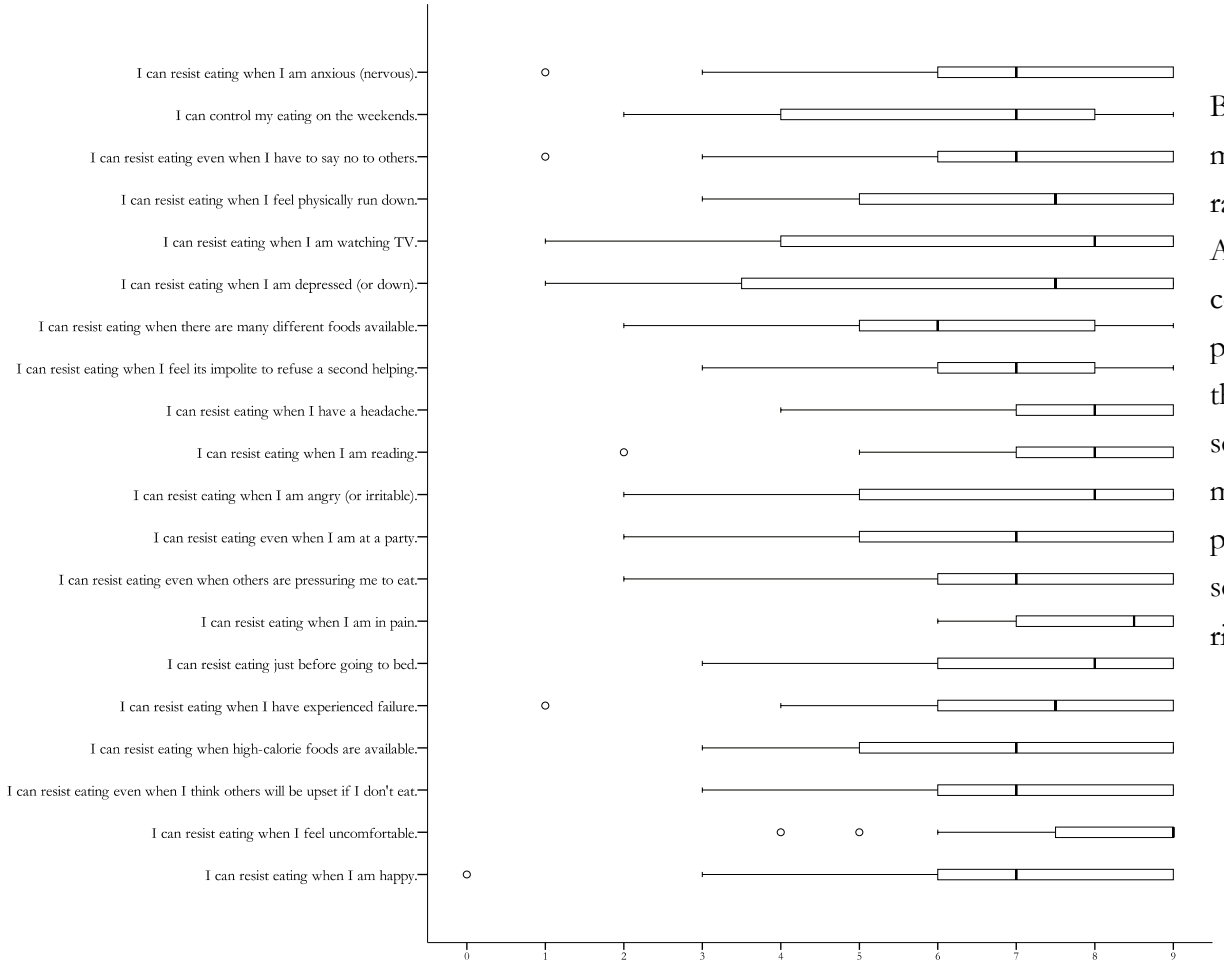


Figure 5.2 Boxplots indicating median and interquartile range for components of the AHEI-2010 scoring method (n=25) Ten is the ideal score for all components. Criteria for scoring are available from Chiuve et al, 2012. PUFA: Polyunsaturated fatty acids



Box plots indicate the median and interquartile range for each measure. Apart from the two comparative risk perception measures that were on a 5-point scale, all risk perception measures were on 7-point scale with higher scores indicating higher risk.

Figure 5.3 Responses to the WEL questionnaire (n=21)

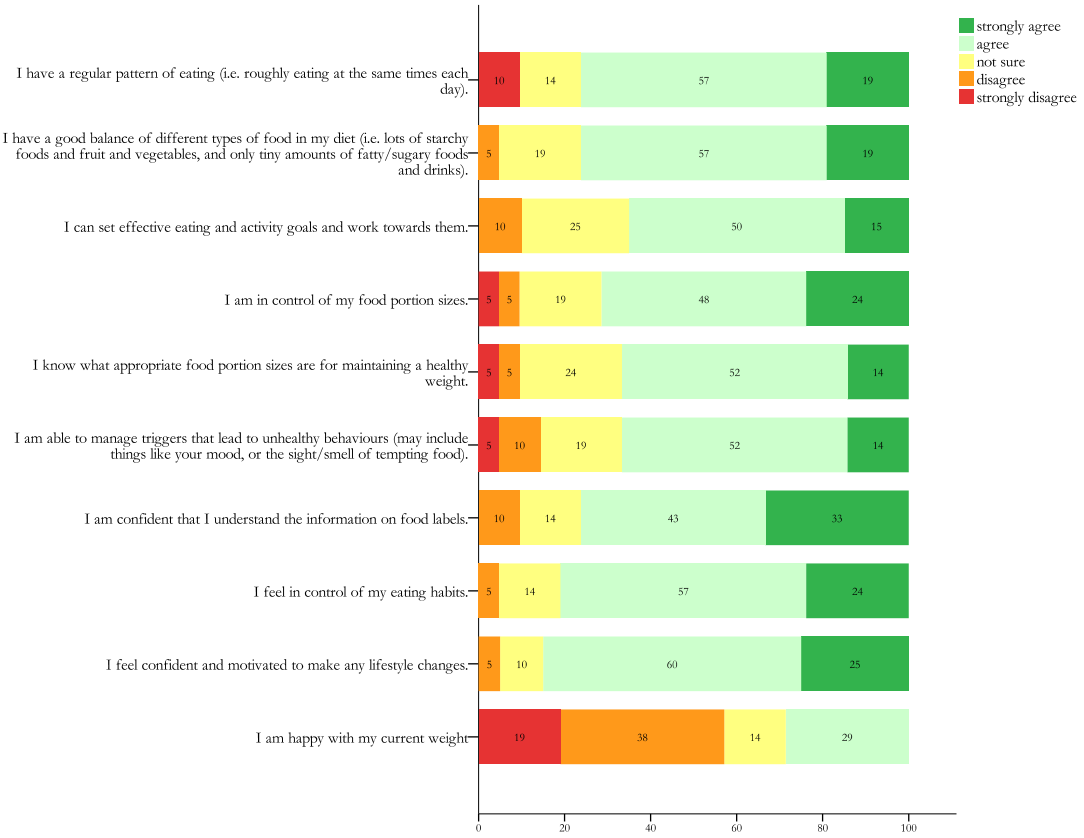


Figure 5.4 Percentage responses to the Shape-Up questionnaire assessing the main constructs of the intervention

5.4.3 Physical activity and exercise preferences

Sixty nine per cent (69%) of participants met the guidelines of at least 30 minutes of physical activity per day, mostly in the form of normal pace walking. A minority reported some vigorous physical activities and/or resistance and stretching exercises (Figure 5.5).

Table 5.3 displays their exercise preferences. About a third of survivors felt they were interested and potentially able to participate in an exercise program. They were mostly interested in walking; being their favourite activity both in winter and summer. The majority (84%) would prefer to start such a program after the end of primary treatment though the timeframe varied from immediately (12%) to one year post treatment (40%). About half of them preferred to exercise at home or in the morning and the majority (84.6%) agreed upon light or moderate intensity activities.

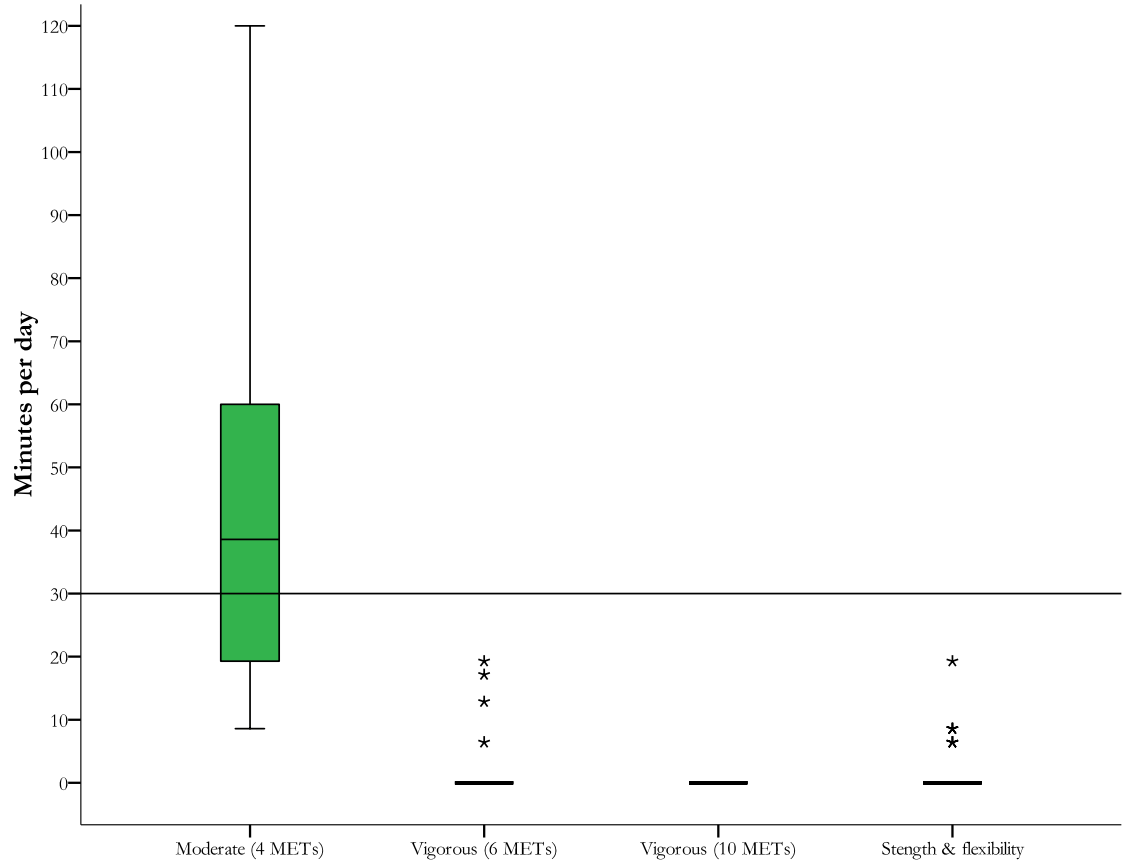


Figure 5.5 Daily minutes of physical activity in metabolic equivalents (METs)[9] in the week before the interview

The horizontal line indicates the guideline of at least 30 minutes of daily moderate physical activity.

[9] Four METs are equivalent to walking at 5.6km/h, six METs are equivalent to leisure cycling at 15.7km/h and ten METs are equivalent to running at 9.6km/h.

Table 5.3 Descriptive statistics of the exercise preferences of study participants

Preference variable	N	%
Would you be interested in an exercise program?		
yes	9	34.6
no	6	23.1
maybe	11	42.3
Able to participate in an exercise program?		
yes	9	34.6
no	6	23.1
maybe	11	42.3
Types of exercise most interested in		
walking	18	69.2
swimming	3	11.5
aerobic	1	3.8
yoga	4	15.4
When would you have preferred to start an exercise program?		
Before treatment	1	4.0
During treatment	0	0.0
Immediately after	3	12.0
3-6 months after treatment	10	40.0
At least 1 year after treatment	10	40.0
No preference	1	4.0
Who would you prefer to exercise with?		
Alone	6	23.1
With other cancer survivors	2	7.7
With friends	2	7.7
With family	5	19.2
No preference	11	42.3
Where would you prefer to exercise?		
At home	14	53.8
At a community fitness centre	4	15.4
At a cancer fitness centre	1	3.8
No preference	7	26.9

Preference variable	N	%
What time of day would you prefer to exercise?		
Morning	12	46.2
Afternoon	5	19.2
Evening	2	4.2
No preference	7	4.2
What is your favourite exercise in the summer?		
Walking	18	75.0
Gardening	4	16.7
Golf	1	4.2
Swimming	1	4.2
What is your favourite exercise in the winter?		
Walking	21	87.5
Swimming	2	8.3
Stationary bike	1	4.2
What intensity would you prefer to exercise at?		
Light	9	34.6
Moderate	13	50.0
Vigorous	2	7.7
No preference	2	7.7
Same or different activity every time?		
Same activity	14	53.8
Different activity	12	46.2
Supervised or not supervised exercise sessions?		
Supervised	17	70.8
Unsupervised	7	29.2
Spontaneous/flexible or scheduled exercise sessions?		
Spontaneous	11	44.0
Scheduled	14	56.0

5.4.4 Anthropometry and body composition

With a mean BMI of 29.5kg/m^2 (SD: 6.99) (Table 5.4), 96.2% of participants were affected by overweight or obesity (Table 5.5). However, based on the FFMI and FMI criteria, one participant (3.8%) with normal BMI was classified as sarcopenic but four of them (19%) regarded themselves as slightly underweight. Furthermore, six (23%) overweight participants based on BMI were classified as having average fat and muscle based on FFMI and FMI criteria. There was excellent agreement between BMI and FFMI/FMI criteria for determining obesity. Interestingly, only 66.7% regarded themselves as slightly overweight or very overweight.

Table 5.4 Body composition measurements (n=26)

	Mean ± SD	Reference
BMI (kg/m^2)	29.5 ± 6.99	
FMI (kg/m^2)	11 ± 4.7	<11.8
FFMI (kg/m^2)	18.4 ± 2.6	>15
%fat	36.2 ± 6.77	>35% for overweight >40% for obesity

Table 5.5 Categorisation of body composition based on FMI and FFMI criteria, BMI, and perception (n=26)

Categorisation by	FMI & FFMI		BMI		Perception (n=21)	
	N	%	N	%	N	%
Sarcopenia / underweight (Low muscle and average fat)	1	3.8	0	0.0	4	19.0
Normal (Average fat and muscle)	6	23.1	3	11.5	3	14.3
Overweight (High fat and average muscle)	11	42.3	14	53.8	8	38.1
Obesity (Very high fat and average muscle)	8	30.8	9	34.6	6	28.6
Sarcopenic obesity (Very high fat and low muscle)	0	0.0	0	0.0	n/a	

The Hattori-style chart (Figure 5.6) also indicated that a given BMI encompassed a wide variability of %fat and muscle mass. The standard deviations in FMI and FFMI are 4.7 and 2.6kg/m^2, respectively (Table 5.4), suggesting the variability in FMI is double of that in FFMI after adjustment for height. The BMI values of the two marked participants in the graph are similar, but those of FMI and FFMI vary significantly, as detailed in the figure legend. When weight change intentions were assessed, about half of the participants classified with overweight or obesity mentioned their intention to lose weight and, surprisingly a minority were trying to gain weight (Table 5.6).

Table 5.6 Weight change intentions by BMI category (n=21)

Are you trying to gain weight, lose weight or neither?						
	Gain weight		Lose weight		Neither	
BMI categories	N	%	N	%	N	%
Normal weight	0	0.0	0	0.0	0	0.0
Overweight	1	8.3	7	58.3	4	33.3
Obesity	1	11.1	5	55.6	3	33.3

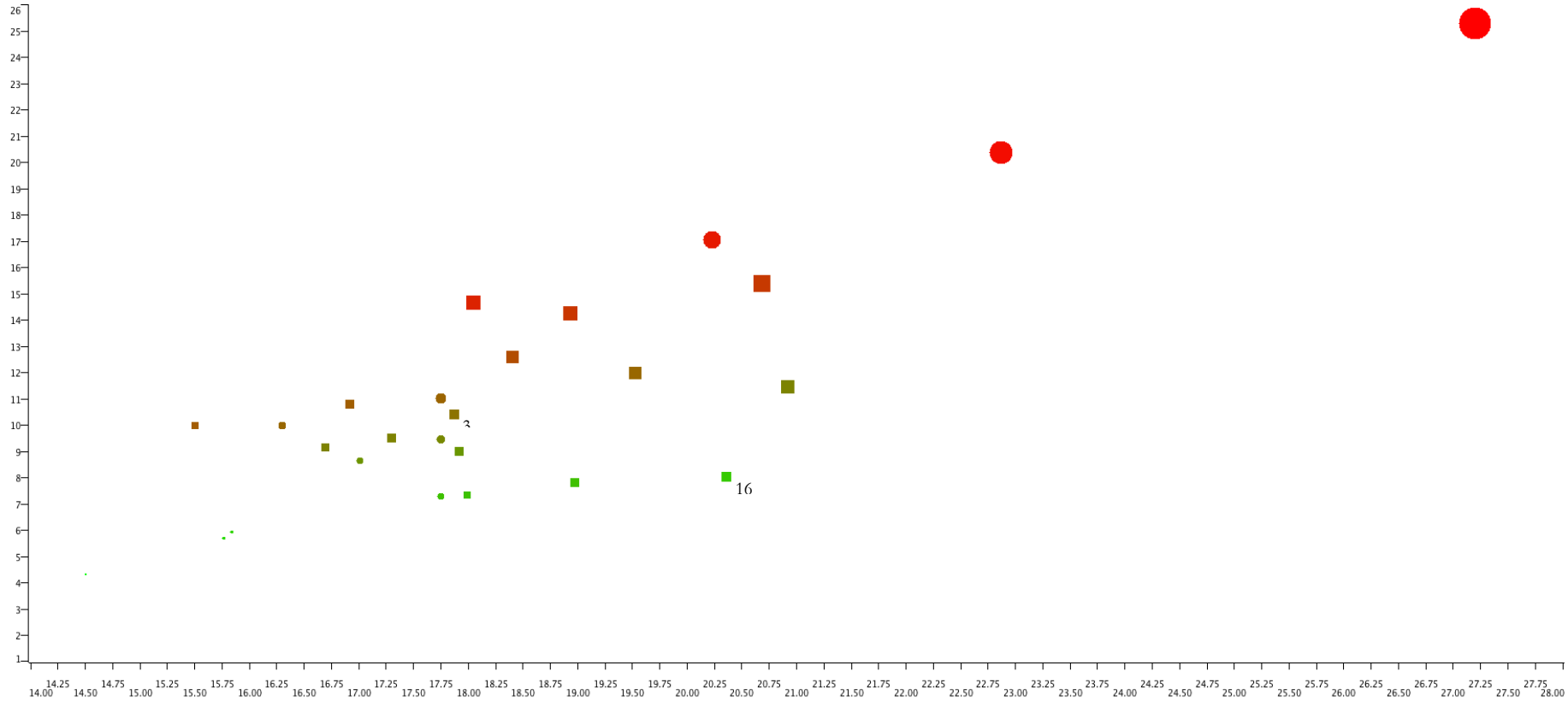


Figure 5.6 FFMI (X axis) plotted against FMI (Y axis) (n=26)

Colour indicates %fat mass (light green indicates lowest %fat and red indicates highest %fat. Size indicates continuous BMI. Shape indicates age (circle for <65 years old and rectangle for >65 years old). Participant 16 has BMI of 28.4kg/m^2 with %fat 28.2%, FMI 8.0kg/m^2, FFMI 20.4kg/m^2. Participant 3 has similar BMI 28.3kg/m^2 with %fat 36.8%, FMI 17.90kg/m^2, and FFMI 10.40kg/m^2.

5.4.5 Worry

Although about half of participants (53%) reported high levels of health-related worry in the past year, primarily small changes in their diet or physical activity due to worry were reported (Figure 5.7).

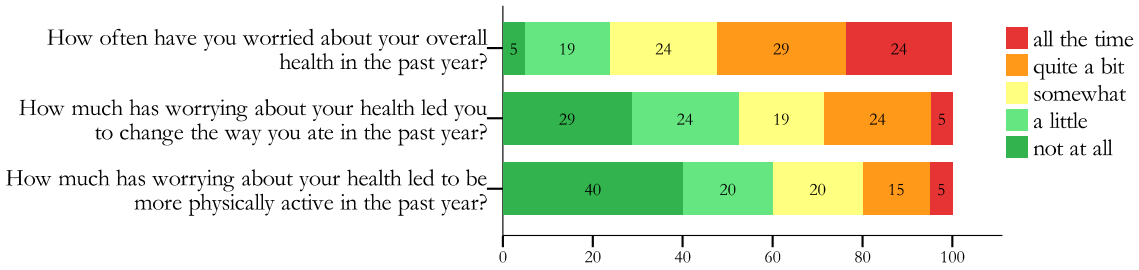


Figure 5.7 Percentage of participants (n=21) reporting worry

5.4.6 Cancer recurrence attributions

Most (≥85%) reported medical check-up, smoking, healthy eating, healthy weight, and physical activity as important or very important factors influencing the chances of cancer recurrence (Figure 5.8). Having a positive attitude, luck, and God's will received ratings that were more diverse but there were still ranked as important or very important by about half of the participants.

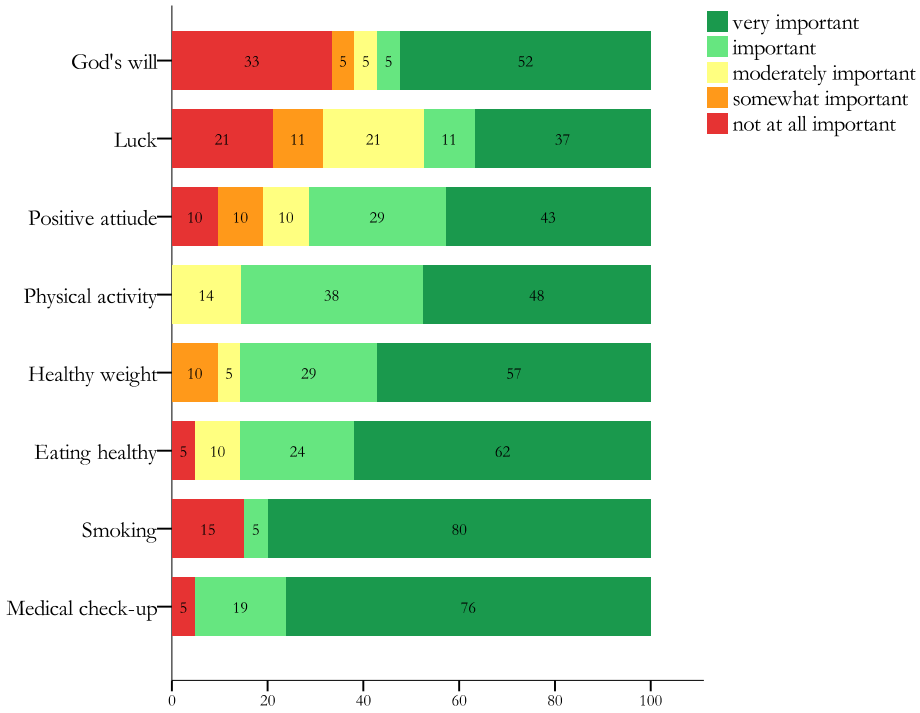


Figure 5.8 Importance of factors influencing recurrence (n=21, % responses)

5.4.7 Risk perception

Participants reported low to average risk perceptions for cancer recurrence or secondary cancer development regarding changes in their physical activity or diet. However, the risk perception score were higher in the comparative risk assessment (Figure 5.9). Many participants found it difficult to understand the concept of risk, especially that of recurrence. Their most common explanation was the difficulty in conceptualising the possibility of womb cancer recurrence given the surgical absence of the uterus. Absolute verbal risk perceptions were positively correlated with respective feeling-of-risk perceptions, ranging from r_s=0.52 – 0.74 (all p<0.02). However, comparative risk perception was not associated with the majority of the rest risk perception measures.

5.4.8 Social support

Most participants reported low to moderate social support for physical activity and healthy eating (Figure 5.10). For example, 57% and 29% of participants reported that their family and friends never did physical activity or ate healthy meals with them, respectively.

5.4.9 Health-related quality of life

Participants scored moderately to highly for their overall health and highly for their HRQoL with median scores of 66.6 (IQR: 58.3 – 91.7) and 83.3 (IQR: 66.6 – 100), respectively. Median scores with interquartile range for the functional and symptom scales sand items are shown in Figure 5.11 and their raw data on Figure 5.12.

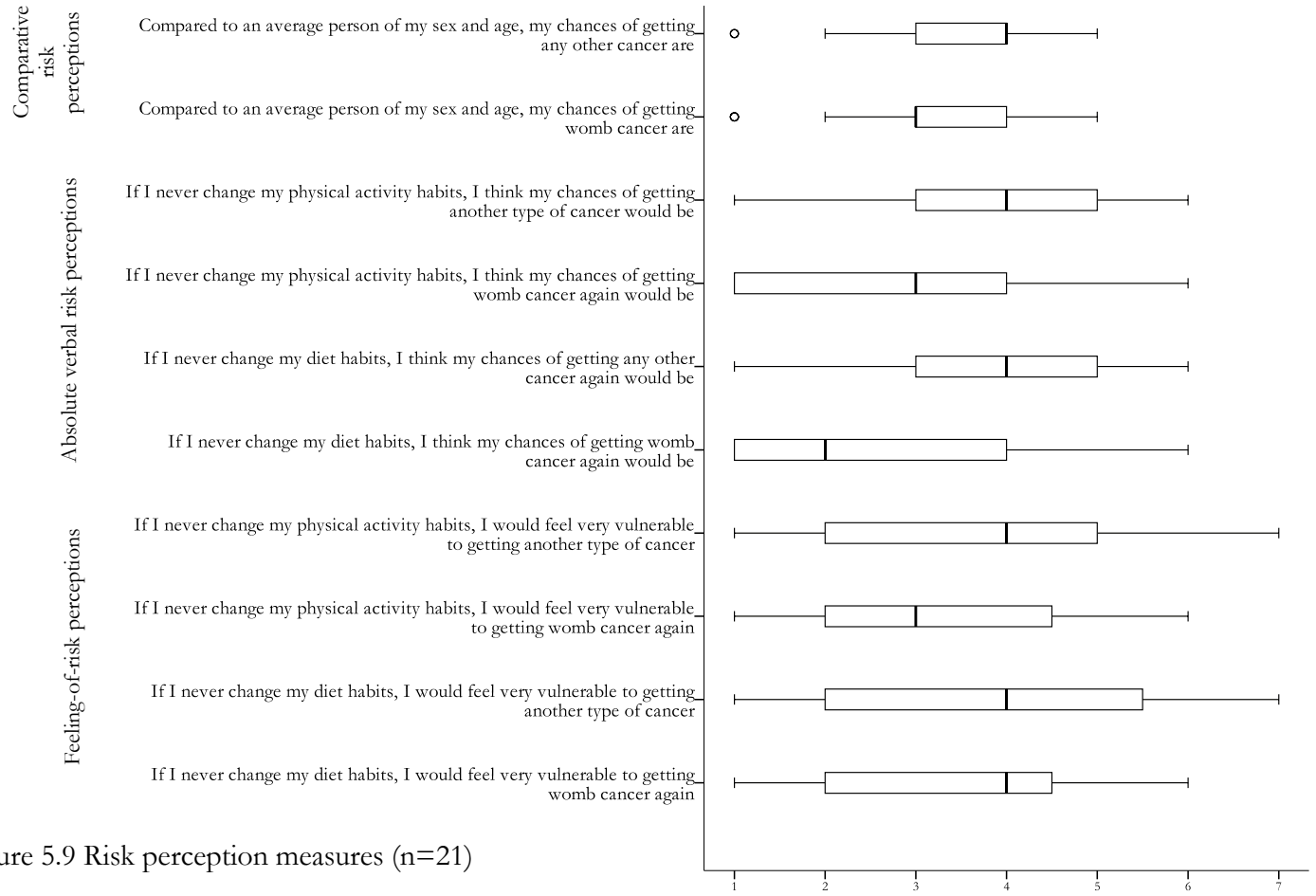


Figure 5.9 Risk perception measures (n=21)

Box plots indicate the median and interquartile range for each measure. Apart from the two comparative risk perception measures that were on a 5-point scale, all risk perception measures were on 7-point scale with higher scores indicating higher risk.

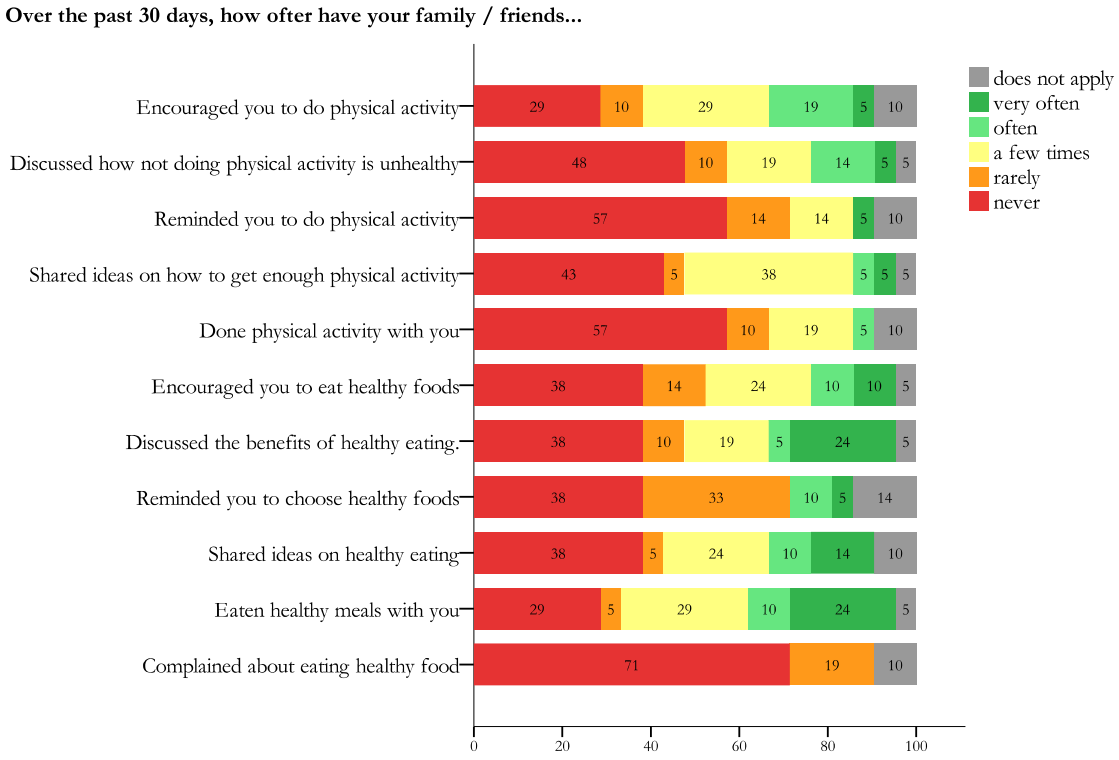
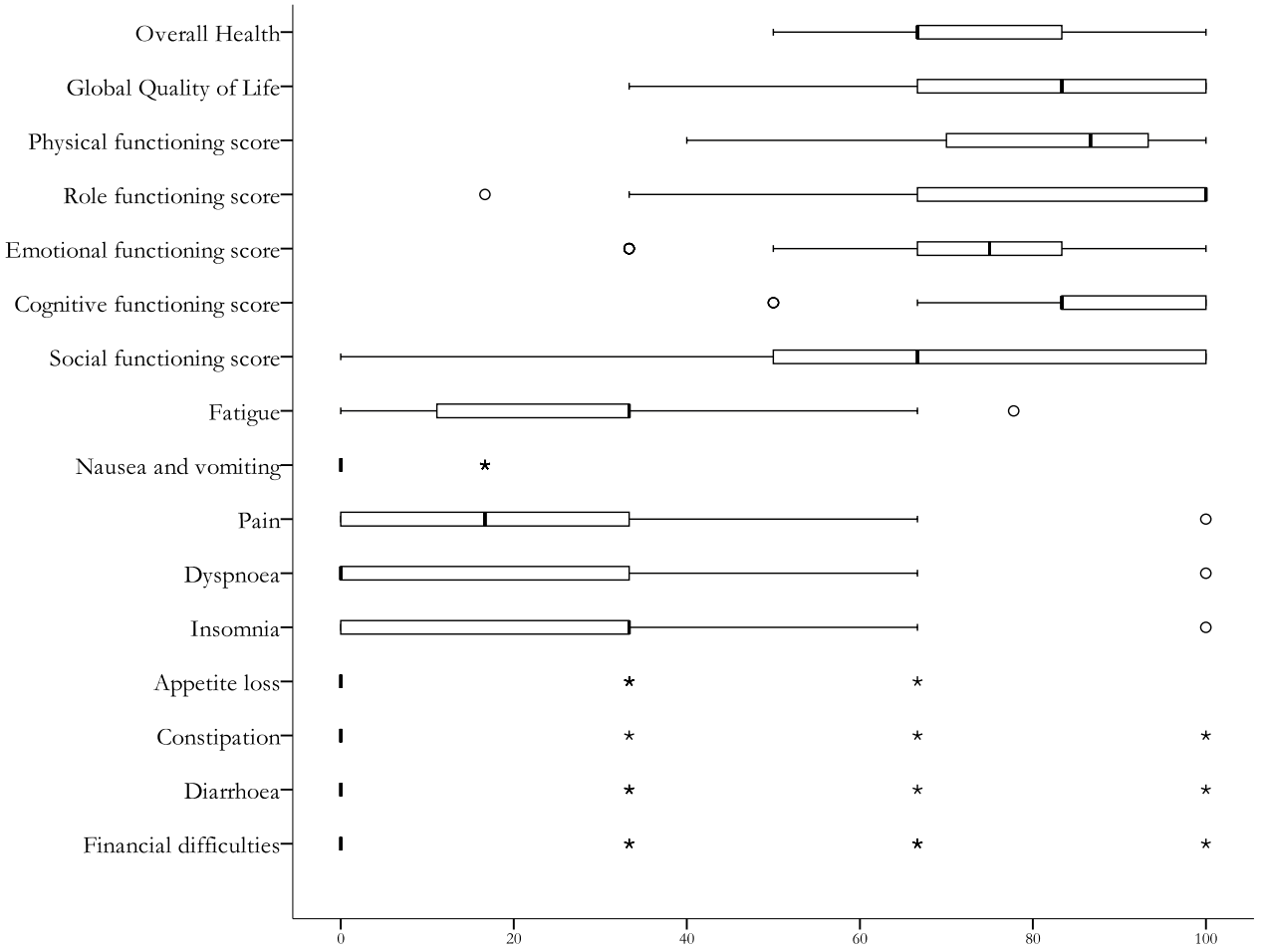


Figure 5.10 Percentage ratings of social support on physical activity and healthy eating

The median score for all but the social functioning score were above 75 indicating a high level of functioning. Fatigue, pain, and insomnia were the most commonly reported symptoms. Participants reported a low level of symptoms specific to endometrial cancer (Figure 5.13). Exceptions included urological symptoms, and muscular pains. As only three participants responded to the sexual activities questions, percentages were not calculated for these variables.



Box plots indicate the median and interquartile range for each score/ scale. Higher scores for the functioning scores indicate higher levels of functioning. Higher scores in the symptom scales/ items indicate higher levels of symptomatology/ problems.

Figure 5.11 (Outcomes of the QLQ-C30 questionnaires (n=21)

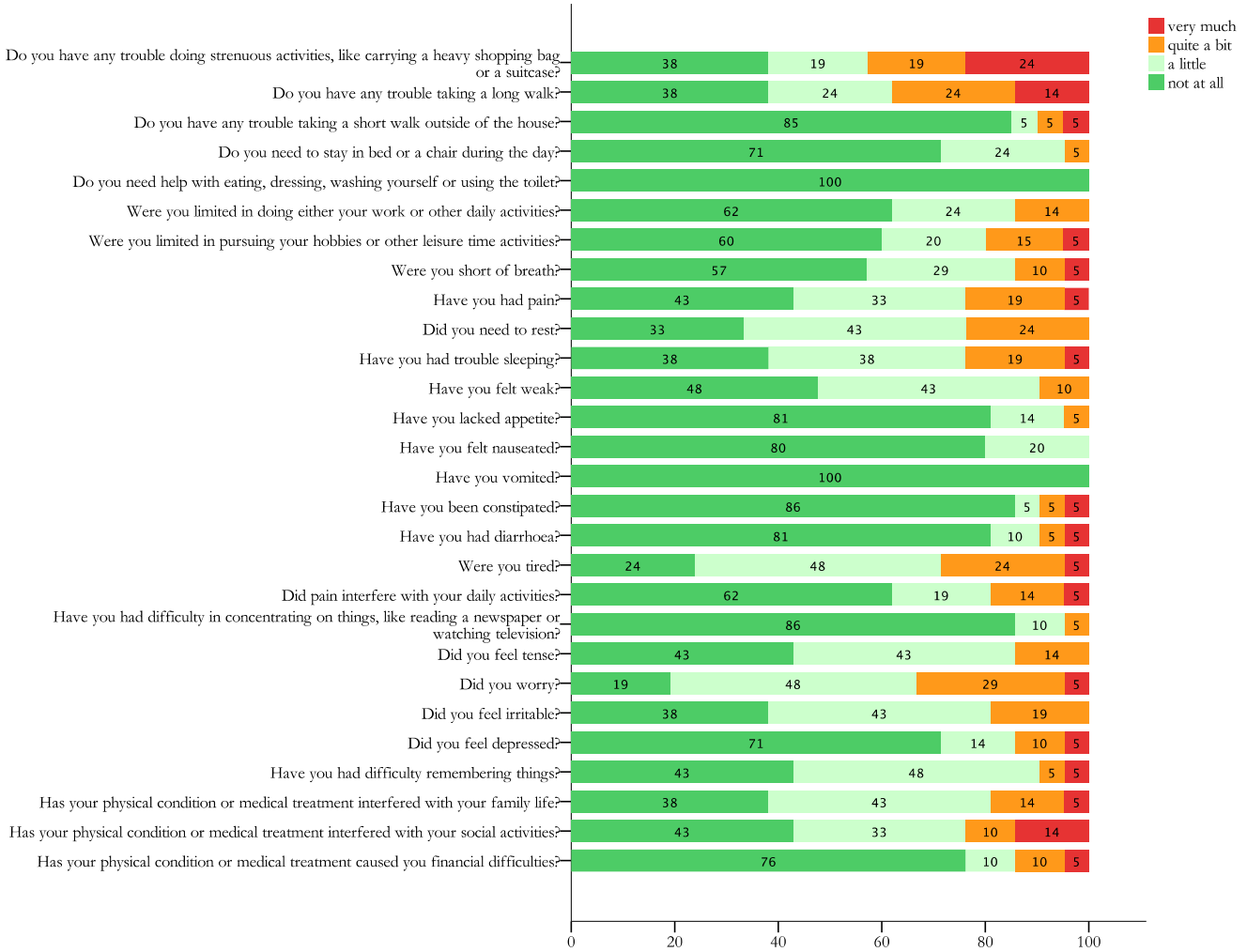
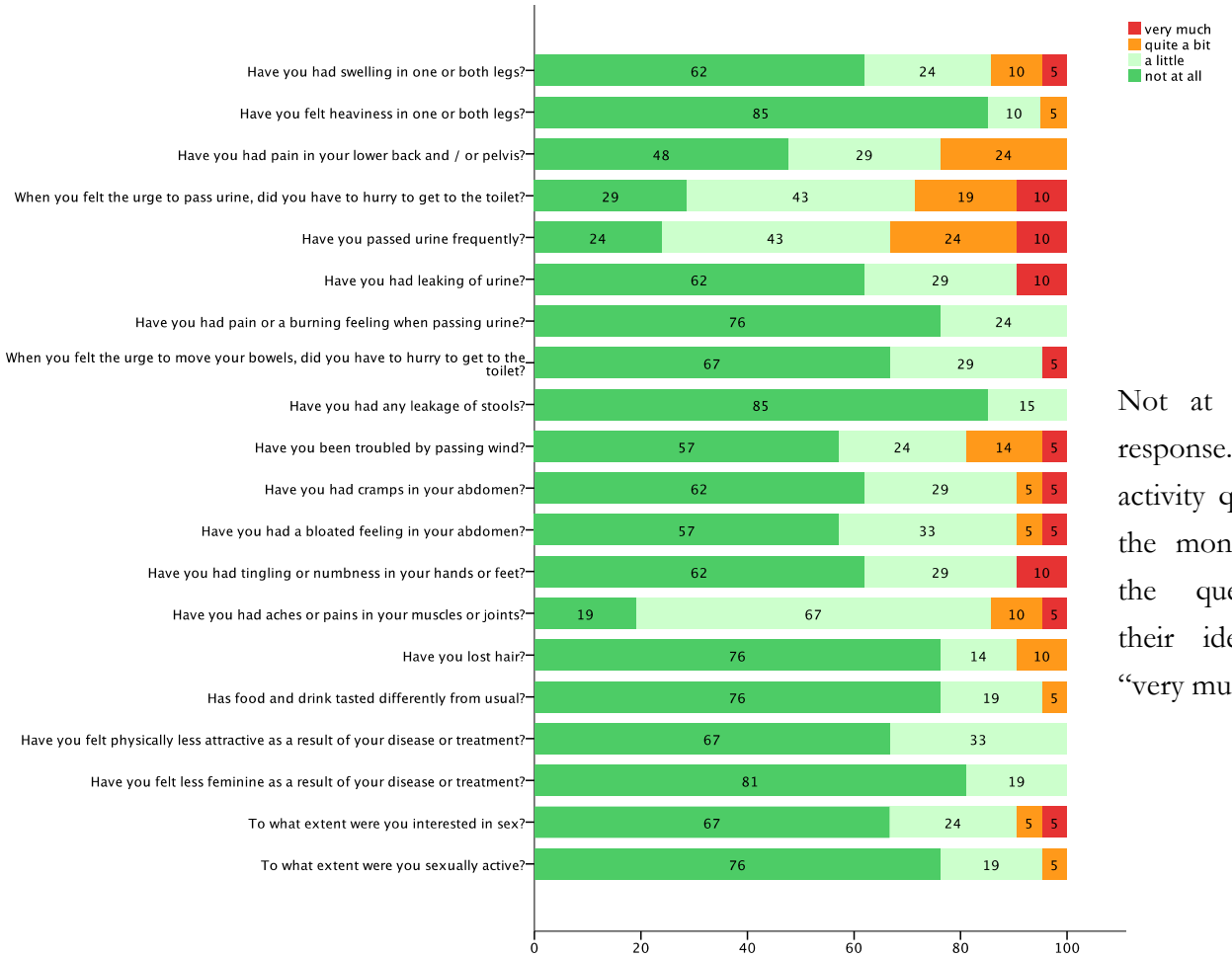


Figure 5.12 Health and wellbeing among participants (n=21) in the week before filling in the questionnaire (percentage responses)



Not at all is the ideal response. The two sexual activity questions refer to the month before filling the questionnaire and their ideal response is "very much".

Figure 5.13 Health and wellbeing among participants (n=21) in the week before filling in the questionnaire (percentage responses)

5.5 Discussion

Endometrial cancer survivors had a high prevalence of overweight and obesity, moderate diet quality, high eating behaviour self-efficacy, and reported meeting the physical activity guidelines. They reported low to average risk perceptions, low social support for health behaviours, and high overall quality of life.

Post cancer diagnosis, the lack of change in the suboptimal fruit and vegetable intake might indicate either a lack of the so-called "teachable moment" or undertaken lifestyle changes were not in line with recommendations. These results are similar to previous studies indicating minor self-motivated lifestyle changes after cancer diagnosis (Williams et al., 2013b). Although no previous studies have assessed diet quality with the AHEI-2010 index in the UK population, an analysis of the Whitehall II cohort using the early AHEI version has indicated similar overall dietary scores to the current study (Akbaraly et al., 2011). In that study, lower adherence to AHEI was associated with increased mortality, indicating the potential of optimal dietary pattern. Previous studies in endometrial cancer survivors have generally assessed only the fruit and vegetable intake as a proxy for dietary quality, with similar (Blanchard et al., 2008) or higher (von Gruenigen et al., 2012) scores for fruit and vegetables to the current study. However, this approach fails to comprehensively assess various dietary constituents that can affect disease risk. Therefore, future dietary assessment should consider an overall dietary approach.

The ASA24 software probably provides the only widely tested user-friendly software for dietary recalls allowing for standardised assessments. Although the software has the potential for self-administration, some participants, particularly those with low computer literacy, might find self-administration demanding and time consuming. Further research in

UK older adults can address these questions. Given the small differences in some foods between the USA and the UK, it was decided that the interviewer would keep a record of the recipes and food not found in the database during the recalls for the trial to improve the accuracy of the data. Currently, the software is being adapted for use in Canada and Australia. Previous focus group research for dietary assessment tools in the UK suggested that participants preferred images for portion size estimation, no pop-ups in the design, and completion time no longer than 30 minutes. This has led to the development of "myfood24", a UK-based tool (Carter et al., 2015). These concerns could have been easily addressed in the context of the ASA24 and that would have provided a uniform assessment method allowing comparability of results across countries. The mean completion time of myfood24 in the pilot studies was 30 minutes (similar to ASA24) and issues around navigation, presentation errors, and failure to find functions in the beta version were improved in the live version (Albar et al., 2015). However, lack of validation, cost concerns, and issues around simplicity and efficiency of the search engine that pertained in the live version of myfood24 led to the decision of using ASA24 for the trial.

The observed disagreement of estimating fruit and vegetable intake from 24-h dietary recall and FFQ was probably due to the distinction in the type of error these instruments present. Findings from the OPEN ("Observing Protein and Energy Nutrition") study that used doubly labelled water (an energy intake biomarker) and urinary nitrogen (a protein intake biomarker) to estimate the structure of measurement error in the two instruments suggest that 24-h dietary recalls have smaller systematic error compared to FFQs but higher within-person random errors. Furthermore, the energy underreporting was approximately 30% and 10% using FFQs and 24-h recalls, respectively, which attenuates the diet-disease relationship (Subar et al., 2003). Recalling bias for long-term periods, the

finite food list, and the relative lack of specificity and detail of the food list account for most of the systematic errors in the FFQs. In contrast, the within-person random error in the 24-hour dietary recalls derives from day-to-day variation in intake. This distinction is particularly important when choosing an instrument because random errors can be minimised by averaging many repeat measures and using standardised measurements, and thus the results will approximate the true value, while systematic errors cannot be corrected unless a reference instrument for calibration is in place (Kirkpatrick, 2011). Practicalities aside, the lack of sensitivity and inability to indicate long-term intake has confined the use of a limited number of currently available biomarkers as validation tools (Satija et al., 2015).

A pooled analysis of five large validation studies indicated that multiple 24-hour dietary recalls have higher validity compared to FFQ or single 24-hour recalls and that BMI positively predicts underreporting (Freedman et al., 2014). Another study indicated that 4-6 24-hour recalls combined with an FFQ provided the most favourable way for reducing measurement error (Carroll et al., 2012). Furthermore, many statistical models have been developed to account for the measurement error and estimate the distribution of usual intake, such as the National Cancer Institute (NCI) method (Tooze et al., 2010). Recommendations for best choice methods exist (NCI, 2014a) and more sophisticated measurement tools, including sensors and cameras, are expected to advance the field (Stumbo, 2013). Meanwhile, critical interpretation of the study results should take into account these methodological limitations.

The WEL questionnaire has been previously used in a lifestyle intervention indicating that the intervention was effective in improving eating behaviour self-efficacy (McCarroll et al., 2013). However, it was deemed prudent not to include the questionnaire in the forthcoming pilot trial given the significant ceiling effects in the current study and the

comprehension difficulties. Furthermore, the high self-efficacy scores in the Shape-Up questionnaire might indicate that the potential perceived benefit from an intervention primarily focusing on self-efficacy might be questionable. However, their reported behaviours were not optimal and it might be that they think they are overly motivated to change their lifestyle behaviours, but when actually faced with implementing the lifestyle changes their motivation might drop.

The results regarding the exercise preferences closely reflect previous research (Karvinen et al., 2006), confirming a preference for post-treatment, of moderate intensity, walking-based physical activity programs. About two thirds (69%) of participants reported meeting the daily moderate activity guidelines but not those for strength and flexibility exercises. This contradicts previous studies in the USA and Canada indicating a low level of physical activity in this population (Karvinen et al., 2006, von Gruenigen et al., 2011, Courneya et al., 2005, Basen-Engquist et al., 2009). Apart from the potential country-specific differences, differences in the measurement instruments might account for the discrepancies. In particular, moderate physical activity was estimated as activities close to walking at a normal pace (excluding strolling) and at a fast pace in the current and previous studies, respectively. Therefore, the current study might overestimate physical activity levels.

A recent systematic review of physical activity questionnaires indicated that most have acceptable test-retest reliability with median correlation coefficients in the range of 0.62-0.76. However, the respective median coefficients for objective criterion validity ranged between 0.25-0.39, with only a few scoring above 0.50, indicating their modest validity for estimating active energy expenditure (Helmerhorst et al., 2012). This error leads to attenuation of the observed associations with outcomes and challenges for establishing

dose-response relationships. For this reason, pedometers and, more recently, accelerometers have been used for objectively estimating energy expenditure and for calibrating the questionnaire-derived measurement error in statistical modelling (Matthews et al., 2013). However, accelerometers do not capture activities such as cycling or weight lifting while other tools such as doubly labelled water and indirect calorimetry are impractical reference methods (MRC, 2016). Thus, combination of measurements tools can facilitate better physical activity measurement.

Based on BMI, the results echoed previous studies highlighting the high prevalence of overweight and obesity in this population (Smits et al., 2014, Oldenburg et al., 2013). However, given the widely established pitfalls of BMI as an obesity proxy particularly in diseased populations (Bosy-Westphal and Muller, 2015, Blundell et al., 2014), the analysis of FMI and FFMI was the first in this population attempting to normalise body composition for height providing the best estimate for reduced skeletal muscle mass and obesity (Bosy-Westphal and Muller, 2015). Sarcopenic obesity (reduced skeletal muscle mass and high fat mass), commonly described in other cancer populations with debilitating consequences (Gonzalez et al., 2014), was not present in this sample of endometrial cancer survivors. Therefore, this population might need health promotion advice rather than the intense nutritional management commonly applied in other cancer populations. As with the general population (Johnson et al., 2014), self-identification of overweight and obesity were not ideal in this sample. This lack of recognition together with the lack of intention to lose weight may hinder participation and adherence in behaviour change interventions and it is worth exploring in future research considering the positive association between weight stigma and weight gain (Jackson et al., 2014a).

To my knowledge, this is the first study aiming to describe perceptions of cancer recurrence and secondary cancer development risks related to diet and physical activity in this population. Body weight status has been linked to secondary cancer risk primarily in breast cancer survivors but relevant data on endometrial cancer survivors are scarce (Travis et al., 2013). Increasing feeling-of-risk vulnerability has been suggested to potentially comprise a useful component in health behaviour change interventions, given its strong correlations with behavioural intentions and attitudes (Dillard et al., 2012). The low risk perception scores might indicate that participants considered they were following a healthy diet and were physically active and that relevant behaviour changes would not influence their future disease risk. This conclusion is further reinforced by the lack of correlation between comparative and the remaining risk perception measures, as the comparative risk perception did not evaluate aspects of diet or physical activity. Given the comprehension difficulties of these measures, further evaluation of the content validity of the measures is warranted together with evaluation of their predictive validity of behavioural intentions and behaviours. Future studies should also evaluate risk perceptions for cardiovascular disease, as this is the main cause of death in this population. Previous studies have also indicated that high social support is positively associated with higher levels of health behaviours (Jackson et al., 2015, Barber, 2013). Given the low perceived social support for health behaviours reported in this sample, social support might be a helpful modifiable construct to be added in the behaviour change interventions.

The high scores on overall quality of life, physical functioning, and role functioning and low scores on the symptom scales are indicative of the post treatment period. The most prominent symptoms, that is fatigue, insomnia, and pain, are in line with previous studies in this population (Smits et al., 2014, Koutoukidis et al., 2015a). Previous physical activity

interventions in cancer survivors have indicated significant improvement in these scores (Mishra et al., 2012). Addressing these symptoms in behaviour change interventions should be incorporated in tailoring the information to endometrial cancer survivors with the potential to increase their positive outcome expectations for increasing their physical activity.

Aiming to reduce bias concerning survivors' recruitment for the trial that may hinder the generalisability of trial's results, it was deemed necessary to cease recruitment for this study in December 2014. Although the recruitment rate was not tracked for this study, recruitment was challenging for a study that involved a single non-invasive one-off visit. Obesity is a convincing factor for the development of the endometrial adenocarcinoma histological subtype (type I) of endometrial cancer. An analysis of 24 studies indicated that diabetes was associated to a similar extent with both endometrial cancer types (I and II) and BMI was associated with both but more strongly with type I, indicating that type II cancers might not be completely oestrogen independent (Setiawan et al., 2013). Therefore, targeting particularly type I cancers (rather than all endometrial cancer types) confers the benefit of prioritising those most probably in greatest risk. From a realistic perspective, targeting both populations will allow for a larger pool of participants and increase the external validity of the lifestyle intervention.

This is the first study to comprehensively examine various constructs of diet, nutrition, physical activity, and quality of life in endometrial cancer survivors using predominantly validated questionnaires. This initial assessment warrants replication in future large cohorts, as it was aiming to assess the feasibility of the procedures rather than provide representative population estimates of these variables. The small sample size has not allowed for powered hypothesis testing and the extent of biases in the descriptive estimates

might be high. Furthermore, response bias could not be estimated. As with other studies using similar recruitment strategies, the potential biases from a healthy volunteer effect are high, together with the low representation of socio-economically and ethnically diverse participants. Although bioelectrical impedance falls behind other techniques like dual-energy X-ray absorptiometry and computed tomography in accuracy, it still provides a practical, non-invasive method of body composition estimation with accepted reliability and accuracy (Ward, 2012). The standardised dietary recalls minimised the bias and the use of a UK food database for the analysis avoided the portion overestimation, particularly for fruits and vegetables, when using the US databases. Estimating mean dietary intake using only one dietary recall is recommended but would have resulted in high measurement error in an examination of the association between dietary intake and a dependent variable.

5.5.1 Conclusion

In conclusion, this study provided an indication of physical activity preferences and suboptimal health behaviours in a population predominantly affected by overweight and obesity but not by sarcopenic obesity. The lack of spontaneous changes in fruit and vegetable intake following cancer diagnosis further reinforces the need for behavioural lifestyle interventions. Addressing the low risk perception about their health behaviours and low social support might increase the effectiveness of tailored behaviour change interventions in this population. These conclusions informed the development of the lifestyle intervention, as described in Chapter 7.

Chapter 6 Attitudes, challenges, and needs about diet and physical activity in endometrial cancer survivors: a qualitative study

6.1 Introduction[10]

The previous chapters discussed the high morbidity and mortality burden of endometrial cancer survivors, together with their suboptimal lifestyle behaviours, despite the widespread perception of the teachable moment of cancer diagnosis. These coupled with the currently scarce health promotion advice in oncology practice (Jernigan et al., 2013, Nicolaije et al., 2012) suggests the need for development of population-specific health behaviour change programs.

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[10] The published version of this chapter is available in Appendix 12 Koutoukidis, D. A., Beeken, R. J., Lopes, S., Knobf, M. T. & Lanceley, A. 2016a. Attitudes, challenges, and needs about diet and physical activity in endometrial cancer survivors: a qualitative study. *Eur J Cancer Care (Engl)*.

Nonetheless, the extent of perceived need for support on healthy lifestyle changes after treatment remains unclear in endometrial cancer survivors. Evidence from survivors of other cancer sites indicates the existence of this need. Example topics include dietary guidance for management of symptoms and reduction of fear for specific foods (Anderson et al., 2013, Williams et al., 2013a, Avery et al., 2014). The diverse treatments and treatment effects across cancers may influence dietary and physical activity determinants suggesting the potential need for tailored lifestyle information needs for each cancer site (Rock et al., 2012). Moreover, it is improbable that these needs will be the same across individuals.

The design and development of behaviour change interventions could be informed by understanding the attitudes of this population towards diet and physical activity. The lifestyle trials reviewed in Chapter 2 and 0 indicate that such interventions are feasible. However, many of such lifestyle trials in cancer survivors encounter difficulties in generalisability and widespread dissemination given the low recruitment rates and moderate adherence rates (Adams et al., 2014). Thus, identification of barriers to enrolment and completion of such interventions can inform their design aiming to improve their feasibility, adherence, and, ultimately, effectiveness. Qualitative research is appropriately placed to explore a range of views and inform such decisions.

In particular, applying a framework can guide such design decisions. One such framework is the person-based approach to intervention development. Using qualitative methods, this is a systematic framework of self-management intervention design (Yardley et al., 2015). This focus on self-management mirrors that of the vision of the National Cancer Survivorship Initiative (DoH, 2010) and, subsequently, positions the proposed framework as relevant in this setting.

6.2 Aims

The aim of this qualitative study was, thus, to explore the perceived importance of health behaviours in endometrial cancer survivors, and the factors influencing adherence to a healthy lifestyle following treatment. A second aim was to examine the current information provision following treatment and preferred method of information delivery in this population.

6.3 Methodology

6.3.1 Participants and recruitment

Endometrial cancer survivors were included in the study if they were within five years of end of treatment, as survivors within the 5-year period are more likely to enrol in lifestyle interventions (Adams et al., 2014). Recruitment was conducted through purposive sampling from three non-NHS support groups. These were the Womb Cancer Support UK, the Eve Appeal Gynaecology Cancer Research Fund, and the Cancer Research UK's Cancer Chat online forum. In addition, I contacted women who had participated in the cross-sectional study described above and had expressed an interest to participate in future research. The aim was to acquire a wide range of views from the target population. Hence, the aim was to continue recruitment until data saturation; consistent with general recommendations (Morse, 2000). The UCL Research Ethics Committee approved the study (project 5245/001).

Written informed consent was provided for publication of individual data. A short questionnaire was distributed to participants before the focus groups and interviews. It aimed to capture their demographics, treatment, and current lifestyle behaviours to aid data interpretation. Participants reported their intake of fruits, vegetables, whole grains, pulses,

alcohol, foods high in fats, foods with added sugars, sugary and/or fizzy drinks, red meat, processed meat, poultry and fish not fried, salty foods, and dietary supplements over the past month with a 13-item food frequency questionnaire based on the WCRF cancer prevention guidelines (WCRF, 2007). Examples and detailed portion sizes were provided. The questionnaire was devised for the study purposes to capture aspects of current nutrition guidelines. Physical activity was assessed with a single, reliable, and validated item (Milton et al., 2011).

6.3.2 Discussion protocol

Similar studies and the literature (Morgan and Krueger, 1997) informed the development of the protocol (available in **Error! Reference source not found.**), with input from the supervisory team and Sonia Lopes, a PhD student conducting similar studies in colorectal cancer survivors. The open questions were about the perceived importance of health behaviours following cancer treatment, barriers to and facilitators of adherence to a healthy lifestyle after treatment, obtained and desired information about a healthy lifestyle, and preferred delivery methods of such information. Prompts were used if required. Piloting of the protocol for acceptability was conducted with two lay subjects.

6.3.3 Procedure

Between July and September 2014, two focus groups (n=5, n=3) took place at UCL. Each audio-recorded group lasted about 1.5 hours. Telephone interview was proposed as an alternative to those unable to attend. Only the participants and the two researchers attended the meetings. Rebecca Beeken and I facilitated the discussions, acting as moderator and note-taker alternately. We encouraged them to discuss their experiences and

thoughts openly. The eight telephone interviews were also audio-recorded, followed the same protocol, and lasted about 30-45 minutes.

Limited guidance exists for appropriate recruitment figures when triangulating interviews with focus groups. Previous studies that have integrated the two techniques for pragmatic reasons have conducted one large focus group (n=7) and one interview (Rees et al., 2003) or eight interviews and a small focus group (n=3) (Memon et al., 2016). Two interviews and one small focus group (n=3) have been used in another study (Taylor, 2005). A predefined aim was to have at least five participants in each focus group. Last-minute dropouts, however, rendered this impossible for one of the groups. The group (n=3) went ahead for pragmatic and ethical reasons.

6.3.4 Analysis

All qualitative data were transcribed verbatim and independently checked against the recordings for accuracy. A six-phase thematic approach guided data analysis (Braun and Clarke, 2006). It aimed to provide a rich description of the data, and to identify themes at an explicit level using a realist approach (Braun and Clarke, 2006). NVivo version 10 (QSR International Pty Ltd, 2014) software was used. I familiarised myself with the data as they were acquired and generated the initial codes. The final coding tree (**Error! Reference source not found.**) was produced following an iterative five-cycle discussion with the supervisory team. Using this tree, Sonia Lopes independently coded 43% of the data (one random focus group transcript and two interview transcripts). High inter-rater reliability was achieved (mean weighted Kappa: 0.96). Minor differences were resolved by discussion. The size of the coded text aimed to capture the true contextual meaning.

Based on the established coding structure, I coded the remaining transcripts. I checked all transcripts against the coding tree for differences. No differences were found which

resulted in a collective analysis of all data. Data from both collection strategies were mutually informative for the conceptualization of the themes. The latter were generated though collation of code names, revision, and refinement so that internal homogeneity and external heterogeneity were maintained. Checks against transcripts ensured that all themes reflect most participants. Individual experiences were also highlighted. Reporting of the results followed standard guidelines. The completed COREQ checklist is available in **Error! Reference source not found.** (Tong et al., 2007).

6.4 Results

6.4.1 Participants' characteristics

Sixteen out of the thirty-four screened survivors took part (Figure 6.1). Socio-demographic and treatment characteristics are shown in Table 6.1. With a median age of 57.4 years, most were White British (81.3%), married (56.3%), and highly educated (53.3%). Table 6.2 presents participants' lifestyle characteristics. Four of them (25%) were affected by obesity. Reported physical activity levels where low compared with guidelines. About half reported meeting the vegetable and whole grain recommendations and 40% those for fruit intake.

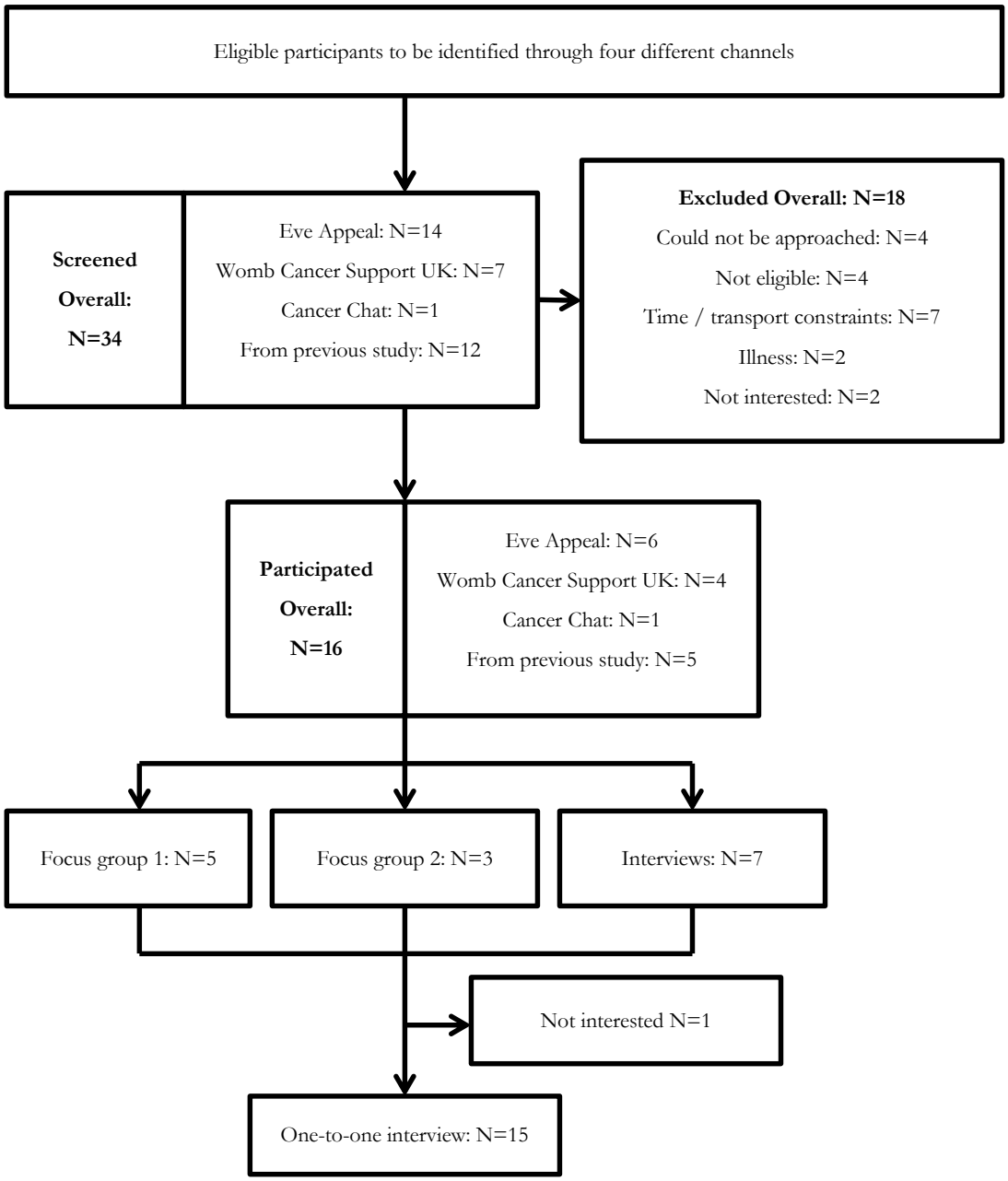

Figure 6.1 Flowchart of participants
Reproduced with permission from (Koutoukidis et al., 2016a).

Table 6.1 Socio-demographic and treatment characteristics of the participants

Socio-demographic characteristics	Total sample (N=16)
Age (years) mean ± SD (range)	57.4 ± 13.2 (33-84)
Ethnicity N (%)	
White British	13 (81.3)
Any other white background	2 (12.5)
Indian	1 (6.3)
Marital status N (%)	
Single/never married	4 (25)
Married / living with partner	9 (56.3)
Married separated from spouse	1 (6.3)
Divorced	1 (6.3)
Widowed	1 (6.3)
Living arrangement N (%)	
Own outright	7 (43.8)
Own mortgage	5 (31.3)
Rent privately	3 (18.8)
Other (e.g. living with family / friends)	1 (6.3)
Highest educational status N (%)	
Degree or higher degree	8 (53.3)
Higher education qualification below degree level	2 (13.3)
A-levels or higher	3 (20)
ONC/BTEC	1 (6.7)
O Level or GCSE (Grade D-G)	1 (6.7)
Employment status N (%)	
Employed full-time	4 (25)
Employed part-time	2 (12.5)
Unemployed	1 (6.3)
Self-employed	2 (12.5)
Full-time homemaker	1 (6.3)
Retired	5 (31.3)
Disabled or too ill to work	1 (6.3)
Treatment characteristics	

Time since diagnosis N (%)	
<1 year	6 (37.5)
1-3 years	6 (37.5)
3-5 years	4 (25)
Treatment N (%)	
Surgery	7 (43.8%)
Surgery & Radiation	5 (31.3%)
Surgery & Radiation & Chemotherapy	4 (25%)

Reproduced with permission from (Koutoukidis et al., 2016a)

Table 6.2 Lifestyle characteristics of the participants

Lifestyle characteristics	Median (IQR) (range)
BMI (kg/m^2)	25.83 (23.1 – 31.8) (17.9 – 62.4)
Vegetable portions/day	2 (2.0 – 3.5) (1.0 – 3.5)
Fruit portions/day	1 (0.4 – 3.5) (0.1 – 3.5)
Wholegrain portions/day	2 (0.71 – 2.0) (0.1 – 3.5)
Alcohol portions/day	0.4 (0.1 – 0.7) (0.1 – 1)
Physical activity min/day	15 (6 – 24) (0 – 30)
Smoking N (%)	
Yes	1 (6.3)
No	13 (81.3)
Used to	2 (12.5)

Reproduced with permission from (Koutoukidis et al., 2016a)

6.4.2 Themes

Three themes emerged from the data: 1) defining a healthy lifestyle; 2) factors influencing diet and physical activity; and 3) needing to search for information. Letters a, b, and c in the quotes indicate received surgery, chemotherapy, and radiotherapy, respectively.

6.4.2.1 Defining a healthy lifestyle

Participants regarded healthy eating and physical activity as integral parts of a healthy lifestyle. However, their definition of healthy lifestyle was broad including mental, sexual, and psychological well-being.

> *I do think a healthy lifestyle has to include your mental health […] alongside what you eat and your exercise. (FG1_3, 55 years, a & c).*[11]

Regarding healthy eating, participants endorsed sensible amounts, and a varied, and balanced diet, with particular emphasis on homemade dishes. On the one hand, vegetables, fruits, whole grains, fish, and alcohol in moderation were specifically mentioned as components of a healthy diet. Legumes were only mentioned by a couple of participants. On the other hand, red meat, processed foods, and sugar were deemed unhealthy choices. Some further mentioned excess salt and the controversy around supplements.

> *Trying not to eat too much in total, trying to eat lots of fruit and vegetables, trying to not eat too much processed food, trying to eat home-cooked food where possible. We have oily fish like salmon once a week (Int_3, 64 years, a & c).*

> *I think we should all, everybody as a whole, should be avoiding processed foods, the likes of McDonald's and that. I'm a firm believer in preparing food from scratch using just fresh products and steering away from pop (FG1_2, 55 years, a & c).*

With reference to physical activity, the frequency and duration were emphasised compared to intensity of activities.

[11] All quotes presented in this chapter are reproduced with permission from ibid..

[Healthy lifestyle is] plenty of exercise, plenty of moving around (Int_3, 64 years, a & c).

It ought to be a balance between food intake, probably very low on any animal product, and some exercise. Not necessarily strenuous and not necessarily building up, body building stuff (Int_5, 53 years, a).

6.4.2.2 Factors influencing diet and physical activity

The teachable moment of a cancer diagnosis was evident in some participants who reported making favourable lifestyle changes but not in others. The factors influencing diet and physical activity behaviours were categorised in four groups as cognitive, physiological, emotional, social, and practical.

6.4.2.2.1 Cognitive factors

Healthy eating and physical activity were deemed crucial determinants of overall health. This reason motivated them to engage in health promoting behaviours, especially after surviving cancer. Example of such lifestyle changes were inclusion of nuts and organic products, cutting down sugar, eating breakfast, or being more physically active

I think healthy eating is important to anybody but especially to me […]. It is a necessity, not a luxury. And I cannot afford to have [low quality food] – I do not know if this is going to help with cancer or not – but you know in my mind the only thing that I am doing that is in my control is the food. You cannot control much else (Int_5, 53 years, a).

In contrast, some found little need for improvements, as they regarded their lifestyle healthy.

It [cancer] made no difference whatsoever. I mean, I just do what I have always done (Int_1, 67 years, a & b & c).

Not only was physical activity regarded as helpful particularly for symptom management, including management of fatigue, constipation, and bladder dysfunction, but it was also seen as an important determinant of health and physical functioning.

[Physical activity] keeps everything moving, and it gets the oxygen and the blood flowing around the body (Int_7, 84 years, a & c).

Others saw maintenance of suboptimal behaviours as part of their return to normality after treatment.

I am overweight, I hardly exercise - I do very little, I have a sedentary job. […] What I've done is I've put it out of my mind and that's it. I don't think about, oh I've had the cancer, I can't do this, I can't do that, I must be careful. I've just gone back to my life and carried on as normal (Int_8, 61 years, a).

Consciousness about dietary choices was high for some following cancer. Examples include putting additional effort in to increase fruit intake and physical activity. They believed that knowledge about healthy lifestyle behaviours could positively shape behaviour.

I am forcing myself to go to [exercise] classes. […] I have made myself start eating fruit, where I have always really hated fruit (FG1_5, 60 years, a & b & c).

Survivors mentioned having behavioural self-regulation systems in place to achieve and maintain health promoting behaviours following treatment.

> *The main problem was not doing too much […]. So, I did it in a systematic way. […] I did what I could. I walked a lot, and then just gradually built up from there (Int_4, 51 years, a).*

Following treatment, two survivors monitored their food intake with diaries. For one, it was a helpful weight-loss strategy. For the other, it was a helpful way of identifying foods that cause symptoms. One participant was also monitoring physical activity with a pedometer for weight maintenance purposes.

> *[Regarding the bowel symptoms] I kept a food diary. I still do keep one. I have kept that over a year and a half, hoping that I might be able to go, 'It's mushrooms.' […] I found it very useful. But I found it difficult originally to keep it in a notebook. […] I found a very good app for the food diary […] and I have started keeping it (FG1_3, 55 years, a & c).*

Others also seconded self-monitoring of food and physical activity as potentially helpful strategies but had not engaged in them. Small, attainable goals and rewards were also regarded as useful ways to maintain health behaviours.

> *I suppose it is goal setting. I think if you are living beyond cancer, you want to have something to look forward to, really, planning activities. A bit like a bucket list but smaller goals, not necessarily big things to do; but perhaps smaller things that you can achieve […]. That's how I deal with it, really (FG1_4, 55 years, a).*

> *I would have to set my own sort of system of rewards, really [to improve my lifestyle] (Int_3, 64 years, a & c).*

6.4.2.2.2 Physiological factors

Some participants reported no changes in their lifestyle pattern due to cancer treatment. For others, their motivation to pursue a healthy lifestyle was in conflict with treatment

effects. For example, fatigue, neuropathy, dizziness, pain, lymphoedema, and bowel symptoms were barriers for exercises like crouching or yoga. Such activities were replaced with others that did not interfere with treatment effects.

> *Before I was diagnosed I was doing four Zumba classes a week. I can't do that… I've got up to two a week. And anytime I try any more, I'm ill (FG1_4, 55 years, a).*

Specific dietary alternations were mentioned due to treatment effects. Cancer-related anorexia was the reason for reduced food intake shortly after treatment. Avoidance of bowel symptoms, particularly after radiotherapy, was achieved through specific dietary changes concerning fruits, cheese, and spicy foods.

> *Before I had all the treatment, I used to eat lots of fruit and things, but I don't eat fruit now. And brown bread, I don't eat much of that either. I eat many vegetables at the moment (FG1_1, 57 years, a & b & c).*

Specifically, fibre avoidance was described as a prophylactic measure. No particular pattern of dietary changes and symptoms was observed following treatment completion. Food tolerances varied widely with reports of both increased and decreased fruit intake; the first for health reasons and the latter as prophylactic measure.

> *It comes and goes. So, I might have a month where I can eat a conventional healthy diet and then there will be two or three weeks where I have to eat only what I can eat, and then you just have to work around that (FG1_3, 55 years, a & c).*

> *So it is almost like I am trying to eat healthily and I want to have the brown sandwiches but I know if I have the brown sandwiches… I am already going to the loo so frequently that it is a risk (FG2_2, 33 years, a & b & c).*

6.4.2.2.3 Emotional factors

Physically activity generally improved mood. Participants reported high preferences for gentle exercises, and walking. They also favoured group activities but found gym-based programs boring.

> *[Physical activity] clearly makes you feel better and it clearly keeps everything ticking over (Int_1, 67 years, a & b & c).*

Furthermore, survivors acknowledged the impact of the cancer-specific emotional experience on their lifestyle.

> *Because often people feel sick emotionally after cancer, I certainly did. And it is surprising how often you feel all right during the treatment but it is at the end of it that it is all sorts of emotional problems and so on. I think particularly exercise is difficult to know about. You think it is more difficult and doesn't necessarily cheer you up that much (Int_3, 64 years, a & c).*

6.4.2.2.4 Practical factors

Eagerness for engagement in cancer charity events was demonstrated, with participation in walks and marathons. Environment-related opportunities, such as weather conditions and infrastructure, and time were deemed determinants of physical activity.

> *I am lucky in that the environment is there; I have a nice run on my doorstep, so I just set off and I run […]. Time is my main pressure for not…, my main excuse for not walking to work, for instance, or not… I think, oh I'll do that later (Int_4, 51 years, a).*

Some reported financial barriers for both gym attendance and purchase of healthy foods.

> *Going to the gym does not appeal; apart from that is expensive. […] I think one of the barriers was initially restocking [on healthier foods]. You know, throwing, change, and restocking. I have spent quite a lot to be honest (Int_5, 53 years, a).*

6.4.2.2.5 Social factors

Social support from family and friends was regarded crucial in their everyday life. Not everyone discussed diet and physical activity issues with their friends and relatives. Role modelling and group exercises were deemed helpful. Motivation from relatives facilitated both every day and structured physical activity.

> *My children wanted to do it [a half-marathon]. They said, "Come on, you do it as well". So I said, "Fine, I will" (Int_1, 67 years, a & b & c).*

Additionally, verbal encouragement and provision of healthy options by relatives facilitated maintenance of high dietary quality.

> *So, my sister, who looked after me, made me eat fruit for breakfast and healthy things (FG1_5, 60 years, a & b & c).*

Nonetheless, one survivor mentioned social stigma related to obesity as a barrier to practising health behaviours.

> *People just assume that I eat loads of chocolate, I eat this, I do this and I do that. Or they'll go, 'Why is she in the gym? Why is she dancing like that with the size of her?' And there's part of me going, oh, maybe I can't go, because it's just that stereotypical thing (FG2_2, 33 years, a & b & c).*

6.4.2.3 Needing to search for information

6.4.2.3.1 Received advice

The main dietary advice received was about bowel symptom management (e.g. fibre elimination) during active radiotherapy treatment. No survivor reported receiving unsolicited healthy lifestyle advice after treatment completion. Despite prompting health professionals for such advice, they received unsatisfactory replies. For instance, a consultant encouraged one participant to simply drink more green tea while another simply advised them to eat healthier. Professionals were generally unaware of relevant support groups.

> *There was no support and no advice of what to do. Because I went into the menopause as well, so I was kind of like saying, well, what can I do for that? They were like: "Well, I don't know. You can go to a health food shop." That is basically how they left me. So, I have had to kind of like research that myself (Int_6, 46 years, a).*

6.4.2.3.2 Information sought

Following treatment, Internet was the primary source for lifestyle information. Nevertheless, participants had difficulty disentangling and selecting trustworthy information, due to time constraints to examine the various potential sources. Advice on sugar, and dairy products was considered confusing, whereas cancer charities' websites were deemed as useful sources.

> *Unless you actually know where to look and what sites are reliable, it is just a mine of information, it puts all kinds of things in your mind, and you do not know which is the best advice to take. I went to the NHS website, because obviously that is generally a trustworthy site, but it did not really give me much information, it just really*

outlines the details of endometrial cancer. There was nothing to say where you could go for some support or anything like that (Int_2, 37 years, a).

I found more information on the Macmillan site than I had from anywhere else, I suppose (FG1_3, 55 years, a & c).

Other sources of information included personal trainers, naturopaths, health food shops, and friends following raw diets.

And also I have a friend who trained recently as a nutritionist and she asked me to be her guinea pig (laughing). She is a naturopathic person. Anyway, their advice seemed to be extreme but it was virtually to eat no white, no refined carbohydrates (Int_3, 64 years, a & c).

6.4.2.3.3 Desired advice, timing, and methods of delivery

Another topic was advice they would like to have received, which included healthy lifestyle, recovery, and symptom management. Additionally, survivors were eager to participate in a lifestyle program tailored to their post-treatment effects. As others believed they already had a healthy diet, they regarded it unnecessary to get involved in a diet-focused program.

And I would have liked to have been invited or told about if there was such a thing [a lifestyle program], or even told to start one (FG1_5, 60 years, a & b & c).

[Advice about physical activity] How long, how many hours, how many minutes? What would be too much? How often a week? I do not know any of these (Int_5, 53 years, a).

Immediately following treatment at their hospital discharge or in their early follow-up appointment were the main time period preferences for receiving healthy lifestyle advice.

They would be happy to be introduced to a relevant program at cancer diagnosis or during treatment. However, attendance at the program was more probable following treatment.

> *It would be nice before you go out of the hospital if someone come around, sat down and say: "We have got this booklet, we think it would be beneficial for you to make the changes" (Int_5, 53 years, a).*

Health care professionals were deemed ideally placed to provide reliable healthy lifestyle information or direct survivors to appropriate services. Patience among other interpersonal skills were reported as crucial for the person advising them.

> *GP's probably the initial person that would be able to assess the situation, but I don't think it's necessarily a GP that needs to continue that support with you (FG2_2, 33 years, a & b & c).*

Preferred mode of delivery for healthy lifestyle advice varied. Personal contact, through group meetings or one-to-one sessions, was highly preferred.

> *It would be a group. It is nice to meet, not to meet and chat necessarily, but to have, you know, other people in the same boat, if you like (Int_5, 53 years, a).*

> *Yes. I think it needs to be a one-to-one, because if they give you a booklet or go on the website, it is so impersonal. If you have a one-to-one then at least you know that someone is concerned and they want to help. It is not so helpful if it is just a paper. I mean, even if they've got it and they talk to you and then they give it to you, I think that would be the best thing (FG1_1, 57 years, a & b & c).*

A significant barrier for session attendance was geographical distance. Participants also preferred a program focused on well-being rather than cancer.

> *So I want it to be specific for me, but I do not want it to be about cancer, I just want it to be about going forward – this has happened to you, this is what you've got, maybe, so try this, because when you've got that, you can still do this, and very specific information (FG1_1, 57 years, a & b & c).*

Convenience directed others to prefer web-based materials or exclusively self-help materials.

> *I would personally like to see it online, I would find that useful. You could just sift through and find what you want. If it was good and fairly detailed advice, I'd be quite happy to look up… it's when I want it (FG1_3, 55 years, a & c).*

6.5 Discussion

For endometrial cancer survivors in this study, healthy lifestyle included every part of well-being. On the one hand, benefits not only to their general health but also specific to cancer were reported as reasons for trying to engage in healthy lifestyle behaviours. On the other hand, only 50% and 12% of participants reported adhering to the nutrition and physical activity guidelines, respectively. Treatment effects impeded both diet and physical activity behaviours. The latter were also influenced by social and practical factors. Insufficient information provision was commonly reported. This was accompanied by a self-directed need to search for such support. Among the wide preferences for lifestyle interventions delivery, immediately post-treatment and in-person advice were the most favoured timing and method, respectively.

Consistent with survivors of other cancer types (Anderson et al., 2013, Avery et al., 2014), the current group rated healthy eating and physical activity highly as means to enhance their well-being and overall health. While significant, these were only two of the aspects of

the perceived broad meaning of a healthy lifestyle. This indicated that other components, such as sexual and mental well-being, are incorporated by survivors within this broad term.

With reference to diet, cancer survivors vary in their interpretation of the meaning of healthy eating (Klassen et al., 2014). Survivors in the current study generally were aware of evidence-based components of a healthy diet (Katz and Meller, 2014). Yet, this was not echoed in their reported dietary intake. Low tolerance for high-fibre foods – mostly among those receiving radiotherapy – might be one of the main reasons for this. Colorectal cancer survivors have reported similar concerns (Baravelli et al., 2009). Thus, advice on managing this treatment side effect was welcomed and could be helpful.

As to physical activity, the high preference for low to moderate activities was consistent with the literature (Hammer et al., 2014, Karvinen et al., 2006). Previously identified physical activity correlates include health status, self-efficacy, prior physical activity, action planning, social support, and motivation, among others (Bauman et al., 2012). The similarities between the current study and the general population suggest that tailoring existing interventions to the particular needs of endometrial cancer survivors, such as management of side effects, may lead to well-accepted and effective lifestyle interventions.

The aforementioned behavioural issues, needs, and challenges can further inform future intervention design. The study indicated that health professionals should initiate the favoured in-person advice. However, health professionals report a perceived lack of benefit from lifestyle, lack of clear guidelines, and lack of time as barriers to provision of such advice (Williams et al., 2015a). These barriers can be reduced with educational and training interventions. This advice should be delivered in the immediate post-treatment period and within reasonable geographical proximity. Regular in-person contact in local community

centres and hospitals together with a hybrid community- and home-based intervention may accommodate well these preferences (Stull et al., 2007).

Another point for the design of lifestyle interventions is the behavioural techniques that are relevant in this population. Following cancer treatment, behavioural regulation techniques were implemented for healthy lifestyle promotion. Although, self-monitoring is sometimes deemed demanding and tedious (Burke et al., 2009), participants regarded self-monitoring techniques, such as food diaries, as potentially useful and helpful. Such techniques have been previously implemented in lifestyle interventions in this population (von Gruenigen et al., 2012). The use of self-monitoring in such interventions is further reinforced by a meta-regression suggesting it is the most effective behaviour change technique (Michie et al., 2009).

As part of the intervention development process, the results have informed the final program design for pilot testing which is detailed in the following chapter. Firstly, health care professionals introduced the program to endometrial cancer survivors following treatment completion. Secondly, the program was framed in line with health promotion rather than cancer or weight loss and focuses on self-monitoring and behavioural goal setting. Thirdly, it included advice for side-effect management, like bowel symptoms and fatigue. Fourthly, it acknowledged other parts of lifestyle, such as mental health, and included relevant resources for survivors' reference.

Both strengths and limitations of this study should be mentioned. It is the first to describe the attitudes, needs, and challenges of this population in the UK. Its exploratory nature requires reproducibility in large population surveys. These can further shed light on the complex behaviours of diet and physical activity (Begg and Woods, 2013, Marteau et al., 2012). Although small, the sample size is akin to similar studies (Meraviglia and

Stuifbergen, 2011). Data saturation has been reached, as new themes were not appearing in the last interviews.

A particular strength of using focus groups was the expression of the extent of participants' experiences through the group interaction. It further allowed the generation of data and insights that are potentially not disclosed in one-to-one interviews (Kingry et al., 1990). Both group interaction and in-depth discussions were prevalent in the focus groups. Complementing the focus groups with interviews reinforced the in-depth experiences. Thus, survivors' attitudes were comprehensively examined (Lambert and Loiselle, 2008). Participant's characteristics and main themes converged between focus groups and individual interviews enhancing data credibility. A potential source of bias was the completion of the questionnaire in advance of the discussion/interview that may have primed their responses.

Survivors were included regardless of their BMI, as the study focused on gathering the breadth of attitudes. While non-White and non-British survivors participated in this study, future research should address if the current results are transferable to survivors across the UK, as the sample was of high socio-economic status, and was well engaged with charities, research, and technology. High interest in diet and physical activity among participants might have skewed the results, as shown by their positive attitudes towards the topic. As with most studies, the healthy-volunteer effect and social-desirability bias in answering the questionnaire cannot be ruled out. This calls for future research to identify if awareness and practices presented above are resembled in diverse socio-economic groups.

6.5.1 Conclusion

To recapitulate, lifestyle interventions in endometrial cancer survivors should be tailored to their treatment-side effects and target barriers of a cognitive, social, and practical nature.

Health care professionals should introduce them to in-person programs delivered immediately following treatment. Adoption of such programs within cancer survivorship care plans should follow feasibility and effectiveness studies demonstrating the current potential of such interventions to improve outcomes. These conclusions informed the development, design, and delivery of the lifestyle intervention, as described in the following chapters.

Chapter 7 Using intervention mapping to adapt a health behaviour change program for endometrial cancer survivors

7.1 Introduction

Evidence presented in the previous chapters indicates that behaviour-change interventions to improve diet and physical activity in endometrial cancer survivors are imperative and welcomed. One of the main reasons for this is that they can capitalise on the teachable moment of a cancer diagnosis and, thus, be more effective than interventions targeting the general population (McBride et al., 2000, NICE, 2014b).

Although the optimal timing of the teachable moment remains debated, the post-treatment period seems optimal for provision of healthy eating interventions (Rabin, 2009). Promotion of physical activity might be independent of timing (Rabin, 2009). The median time since diagnosis of accrued survivors was 3.1years in ten physical activity trials (Stacey et al., 2015). Nonetheless, time since diagnosis in long-term cancer survivors (>5 years since diagnosis) is a negative predictor of willingness to participate in health behaviour

trials reduces (Adams et al., 2014). Qualitative data in the previous chapter also support the post-treatment period as the most appropriate time to intervene. While in a vital position to do so, lifestyle advice from health care professionals is scarce (Weaver et al., 2013), particularly given time constraints. Thus, interventions with proven feasibility and effectiveness are needed to foster implementation of lifestyle recommendations.

Furthermore, planning and development of theory- and evidence-based behaviour change interventions with a systematic framework enables a thorough understanding of factors associated with change. This approach also promotes prevention of type III errors, namely failing to demonstrate effectiveness of a program due to weak design or implementation.

7.2 Theory use in health behaviour change interventions

Use of theory [12] for the development and implementation of behaviour change interventions has been proposed as a means of increasing their effectiveness (Glanz and Bishop, 2010). Moreover, use of theory in their evaluation can provide insights into the mediators of behaviour change that can, subsequently, translate to successful interventions. However, the evidence substantiating this case is limited. A meta-regression from the overall literature on diet and physical activity interventions indicated no significant differences in the effectiveness of theory-based interventions compared to non-theoretical interventions (Prestwich et al., 2014). Inadequate intervention reporting may partly account for this. Indeed, only 10% of the 107 theory-based interventions reported associating all

[12] Theory is defined as a "systematic way of understanding events, behaviours, and/or situations" (Glanz and Bishop, 2010).

behaviour change techniques (BCTs) [13] with the respective theoretical constructs and 9% reported addressing all constructs within a theory with BCTs. Of note, better reporting was associated with larger effect sizes when the seven well-reported studies were compared against the 83 with the poorest reporting. Furthermore, use of established BCTs seems to increase intervention effectiveness (Greaves et al., 2011). Therefore, assessment of the application of theory within intervention development and evaluation is critical in future studies. The field of cancer survivorship is in particular need of such assessments given the boost in lifestyle interventions being developed particularly for this population.

Social-cognitive theory (SCT) is one of the most widely used theoretical models for health promotion and one of the most widely used in lifestyle interventions for cancer survivors. It is also the only theory used in the lifestyle interventions in endometrial cancer survivors, as reviewed in Table 4.4. Social-cognitive theory emphasizes effective self-management of individual's health behaviour rather than in the provision of medical care; the two dynamic aspects of health practices. This is crucial for the following reasons. The increasing number of (endometrial) cancer survivors and their high survival rates push the balance of the equation between medical care provision and individual needs towards the latter. This will eventually entail a huge financial burden for the health sector (Hawkes, 2015). Therefore, fostering the practices of individuals is more cost-effective and a high social value option. This is also supported by the National Cancer Survivorship Initiative, which recommends self-management as an integral part of survivorship care, including lifestyle changes (DH, 2013b).

[13] A BCT is defined as an "observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour; that is, a technique is proposed to be an "active ingredient"" (Michie et al, 2013).

Social-cognitive theory encapsulates a set of behavioural determinants, the way they work, and how they can be translated to effective practices. The determinants are illustrated in Figure 7.1 (Bandura, 2004). A description of each construct and their relationship is provided in the aforementioned reference.

According to the model, self-efficacy beliefs, i.e. the personal perception of control affects behaviour both directly and indirectly by the mediation of facilitators and impediments, goals, and expectations. The successful behaviour is the product of the self-efficacy beliefs after accounting for the degree of potential challenges. An important asset of this theory against others is the provision of the mechanisms to change health behaviour. Raising perceived self-efficacy beliefs seems vital for health behaviour change, being strong mediators between knowledge and behaviour (Rimal, 2000). The theory recommends a health promotion program be informative; facilitate social and self-management skills; strengthen the efficacy belief; and create social support. Importantly, these concepts are complementary to each other and may be of little value if one of them is excluded from an intervention.

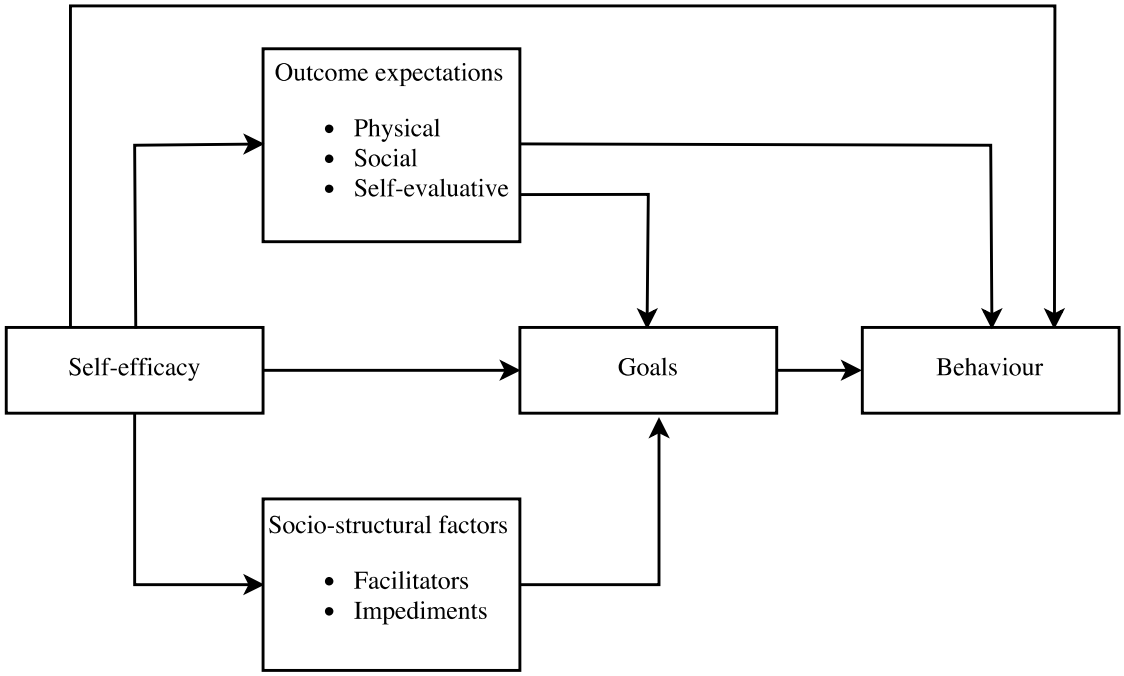

Figure 7.1 Relationships between Social Cognitive Theory constructs. Adapted from Bandura, 2004.

Using SCT, a recent home-based intervention aiming to increase exercise in endometrial cancer survivors demonstrated statistically significant increases in exercise minutes, cardiorespiratory fitness and quality of life domains. As assessed by the SF-36 tool and described in Table 4.4, significant changes were reported for general health, physical function and pain (Basen-Engquist et al., 2014). These are consistent with the overall findings in the literature. Although the changes in physical activity achieved were quite small, especially among the obese participants, they resulted in clinical benefits. An analysis of the theory's constructs showed that both short-term and long-term self-efficacy predicted initiation and duration of exercise, but other constructs were not associated with behaviour (Basen-Engquist et al., 2013). It therefore indicated the importance of targeting self-efficacy for increasing physical activity.

The other lifestyle trial in endometrial cancer survivors was a group-based healthy eating and physical activity intervention grounded in SCT. It aimed to improve participants' self-efficacy by using short-term goal setting to achieve a 5% weight loss in six months (von Gruenigen et al., 2012). The trial results are also presented in Table 4.4 and discussed in 0. The study measured negative emotions, availability, social pressure, physical discomfort, and positive activities as factors associated with self-efficacy. It showed that the intervention group had higher self-efficacy compared to the control group at 6- and 12-month follow-up (McCarroll et al., 2013) but the low quality of reporting (e.g. lack of reporting of baseline data for self-efficacy, lack of reporting of handling missing data, lack of reporting of type of analysis) does not allow for firm conclusions.

A recent systematic review of SCT behaviour change interventions in cancer survivors highlighted their effectiveness, particularly in improving physical activity immediately post-intervention but also for promoting dietary change (Stacey et al., 2015). However, their long-term effectiveness was unclear, particularly due to lack of data availability. The review further noted the inadequate reporting in trials of how the specific SCT constructs (i.e. self-efficacy, barriers and facilitators, outcome expectations, and goals) have been operationalised. These findings were paralleled by another meta-analysis of 14 behaviour change physical activity interventions in breast cancer survivors demonstrating moderate effectiveness immediately post-intervention (Bluethmann et al., 2015). Subgroup analysis also demonstrated rather similar effect sizes between interventions with supervision of high ($g=0.69$) and medium intensity ($g=0.56$), while low intensity interventions produced smaller effect estimates ($g=0.23$). This result indicated the effectiveness potential for less resource-intensive interventions, which might increase their wider applicability. Moreover, most of these 14 studies reported an inadequate application of behavioural theory with the

degree of theory use to get positively associated with intervention effectiveness (Bluethmann et al., 2016).

A recent mediation analysis of an 8-week, SCT-based, lifestyle behavioural intervention assessed the mediation effect of the SCT constructs (self-efficacy, outcome expectations, barriers, social support, and goals) on the association between program participation and pedometer-measured physical activity (Stacey et al., 2016). While self-efficacy and goal setting increased at 20-week follow-up, only behavioural goal setting was a significant mediator of step count. Based on the results, the authors argued that self-regulation models might better fit intervention development for cancer survivors compared to SCT. Nonetheless, the interpretation of the results is limited because of the small changes in SCT constructs probably owing to selection bias, the lack of valid measures for measuring theoretical constructs, and the lack of measures of SCT constructs for healthy eating.

Taken together, these data suggest the potential usefulness of theory in behaviour change interventions in endometrial cancer survivors and the importance for detailed reporting of theory application and evaluation. Taxonomies (standardized definitions and labels for intervention components) are well placed to characterise behaviour change interventions and, consequently, to identify their active components (Michie et al., 2013). These have facilitated the understanding of the mechanisms of behaviour change interventions. A systematic review and meta-regression of effective techniques for healthy eating and physical activity identified self-monitoring paired with at least one additional technique from Control Theory to be significantly more effective compared to other interventions (Michie et al., 2009). Prompting intention formation, goal setting, provision of feedback on performance, and reviewing behavioural goals comprise the additional techniques of control theory.

According to Control Theory, the environment provides the control system with input (perceptions) that is then combined with the existing perceptions of the system (Figure 7.2). The perceptions (input) are compared against a "reference state". The difference between them will drive the output (behaviour). The behaviour then directs the perception (input) with or without the influence of the environment. The behaviour output will vary aiming to negate the difference between the reference state and the perception (input) (Carver and Scheier, 1982). The theory provides a useful framework of understanding health behaviour change, as the comparison between the current state and the "reference state" can elicit desirable behaviours if differences exist. Currently, this theory is referred to as self-regulation theory (Rasmussen et al., 2006).

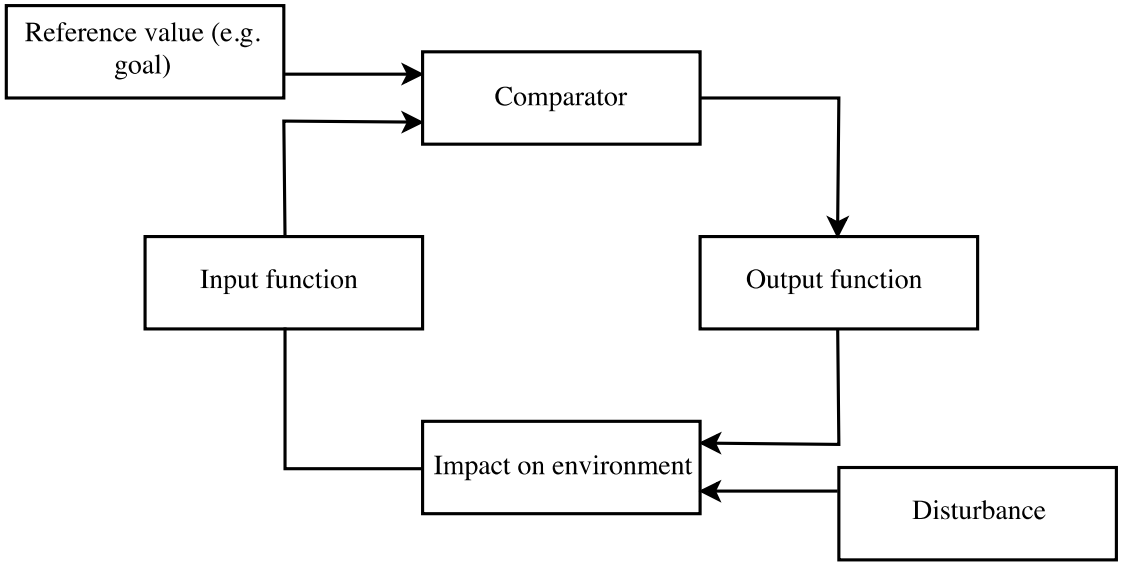

Figure 7.2 Representation of the negative feedback loop in Control Theory. Adapted from Carver and Scheier, 1982.

Other promising BCTs include facilitated social comparison, action planning, providing information about the consequences, providing rewards, time management, behaviour relapse prevention, use of follow-up prompts, problem solving, and planned social support.

(Michie et al., 2009, French et al., 2011, Greaves et al., 2011). Guidelines suggest that individually-tailored strategies, such as self-monitoring of behaviour and progress, stimulus control, goal setting, social support, assertiveness, cognitive restructuring, reinforcement of changes, and relapse prevention are effective behaviour change components (Cavill and Ells, 2010). NICE guidance suggests addressing problem solving, goal setting, how to carry out a particular task or activity, planning to provide social support or making changes to the social environment, self-monitoring of weight and behaviours that can affect weight, and feedback on performance (NICE, 2014b).

Most interventions have focused on targeting reflective processes, such as self-monitoring of behaviour, while most behaviour, including diet and physical activity is automatic (Marteau et al., 2012). Other behavioural determinants, such as habits, might therefore need consideration for inclusion in such interventions. Another meta-analysis is in line with this demonstrating that the habit-behaviour correlation (r=0.45) was of similar-size to that of other behavioural determinants such as intention, control, and affect (Gardner et al., 2011). However, such approaches might not be efficacious in populations of lower socio-economic status, which includes most endometrial cancer survivors, because they do not seem to have a regular everyday pattern of life (Grzywacz et al., 2004). Therefore, trying to apply a model of repeated exposure and action (habit) might not be widely applicable in this population.

7.3 Mode of delivery of behaviour change interventions

The overall literature on nutrition and physical activity interventions has not yet clearly determined the relative effectiveness of the following intervention characteristics: delivery mode, setting, provider, age and ethnicity of the targeted group (Greaves et al., 2011). Data from the US suggest that breast and prostate cancer survivors largely prefer to receive

mailed lifestyle advice (53%) compared to clinic-based advice (10%) (Stull et al., 2007). Specific data on endometrial cancer survivors are lacking. Previous effective, large-scale lifestyle interventions in cancer survivors have used various designs, primarily resource intensive, as their aim was to establish efficacy. For example, the RENEW trial was a home-based trial with personalised materials, telephone counselling, tailored progress reports, and incentivisation to complete the study assessments for a total cost of $1000 per person (Morey et al., 2009, Snyder et al., 2009). The FRESH-START intervention included "a workbook and a series of six four-page newsletters delivered every seven weeks and personally tailored on type of cancer, cancer coping style, race, age, self-efficacy, stage of readiness, and barriers and/or progress toward goal behaviour" (Demark-Wahnefried et al., 2003). Although formal cost-effectiveness analyses have not been performed, resource constraints may render the dissemination of these efficacy interventions in "real-world" settings improbable.

A recent meta-analysis of 22 pragmatic lifestyle interventions involving 5,500 participants (range of mean age and BMI across studies between 38-65 years and 25-37kg/m^2, respectively) for diabetes prevention, which included counselling sessions of varied duration and intensity, showed their effectiveness in improving many biomarkers of cardiovascular disease and diabetes risk (Dunkley et al., 2014). Pragmatic programs like these tailored to the special physical and psychological needs of endometrial cancer survivors might prove both effective, and practical to implement, as social support seems to increase intervention effectiveness (Greaves et al., 2011).

A particular asset of this design is exploitation of the concept of homophily, namely the inclination of social network members to be similar to one another. Health behaviour adoption has been shown to be significantly increased in homophilous networks compared to non-homophilous ones (Centola, 2011). Furthermore, the likelihood of health behaviour

adoption was higher in obese participants who interacted with individuals with similar health characteristics compared to interaction with random individuals (Centola, 2011). Therefore, a group-based intervention with cancer survivors may enhance the effectiveness of the intervention, particularly in those most in need. It may, furthermore, help meet the need for social support, as documented in the literature (Burg et al., 2015).

The cost-effectiveness of the intervention also merits consideration. A recent lifestyle seven-session trial comparing a live and web-based design showed no differences in effectiveness between groups but significantly higher cost-effectiveness of the web-based arm (Keyserling et al., 2014). Telephone-based interventions might also provide a feasible (Grimmett et al., 2014) and potentially cost-effective alternative. However, the LISA telephone-based lifestyle intervention in cancer survivors involved nineteen telephone contacts from highly trained coaches (Goodwin et al., 2014). Again, this might not be feasible for wide dissemination, although data on cost-effectiveness were not reported. An important advantage of the telephone-based and mail-based interventions is the potential wider reach of survivors that might not respond to travel and time commitments required by the group-based design.

7.4 The Shape-Up program

The original plan for this PhD was to evaluate a healthy lifestyle program, called "Shape-Up", in this population. The program details are presented in the following sections. In brief, this is theory-based, behaviour change program for weight management that has been favourably evaluated (Rapoport et al., 2000). It primarily focuses on helping service users improve dietary and physical activity behaviours rather than weight loss through various BCTs. It is already implemented within the NHS indicating its potential feasibility

and acceptability for endometrial cancer survivors. However, both detailed reporting of the BCTs and assessment of the application of theory in the program were lacking.

7.5 Aim

The aim of this chapter was to formally evaluate the use of theory in "Shape-Up" and adapt the program to the needs and preferences of this population with input from potential service users.

7.6 Methods

IM Adapt is a version of Intervention Mapping (IM) to systematically adapt evidence-based interventions. IM is a six-step framework for developing theory-based and evidence-based health promotion programs. The basis of the adaptation process lies in the comparison of the logic model of change of the original program with the needs of the new population. The IM Adapt steps are presented in Figure 7.3.

7.6.1 Needs assessment, organisational capacity, and logic models (Step 1)

Following an assessment of organizational capacity and goals, the adaptation process included a needs assessment examining the health and quality of life issues in endometrial cancer survivors and their association with lifestyle behaviours. These were conducted through an overall review of the literature, the two systematic literature reviews, the exploratory cross-sectional study, and the qualitative study presented in Chapter 1 and Chapter 2, 0 and 0, Chapter 5, and Chapter 6, respectively.

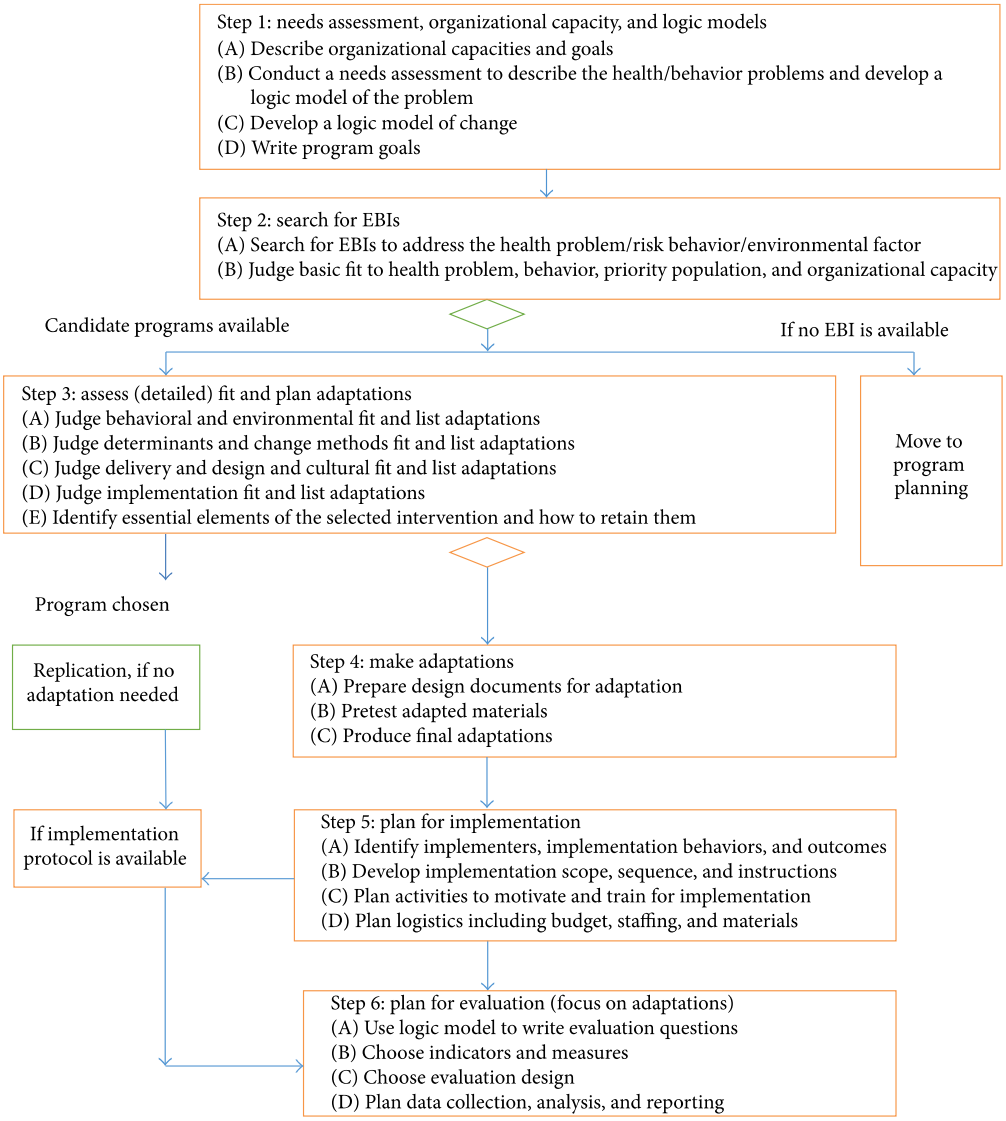

Figure 7.3 The IM Adapt Framework to adapt evidence-based interventions. Reproduced with permission from (Highfield et al., 2015)

Subsequently, a logic model of the problem was created which linked the behaviours with the health problems and HRQoL (Figure 7.4). This formed the basis for the development of the logic model of change that illustrates how the theoretical change methods influence the behavioural determinants that, in turn, affect the behaviours and, finally, health and HRQoL (Figure 7.5). The performance objectives represented observable subsets of the targeted behaviour and the change objectives described what participants must learn or change to meet or maintain the performance objective. Given the organisational capacity,

the models were only focused on shaping the behavioural aspects of the problem. Lastly, the detailed programme goal was established. Based on a meta-regression of effective techniques for healthy lifestyle promotion (Michie et al., 2009), SCT and Control Theory guided the adaptation of the intervention.

7.6.2 Search for evidence-based interventions (EBIs) (Step 2)

While the "Shape-Up" program had been the initial choice, a retrospective search for other evidence-based interventions was run to confirm that no better option existed. PubMed and the Internet were briefly searched for available self-help materials on diet, nutrition, and physical activity in cancer survivors. Databases of effective interventions were also searched for healthy eating, physical activity, or survivorship programs in adults that were tested in an RCT with at least two follow-up assessments. These included the National Cancer Institute (NCI) Research-tested Intervention Programs (RTIPs) database[14] and the Centre for Training and Research Translation (Centre TRT) database.[15]

Furthermore, the basic fit of the chosen program and its acceptability was assessed by providing the focus group participants (0) with the "Shape-Up" booklet at the end of the discussion and prompting them for their initial thoughts.

[14] http://rtips.cancer.gov/rtips/

[15] http://www.centertrt.org/

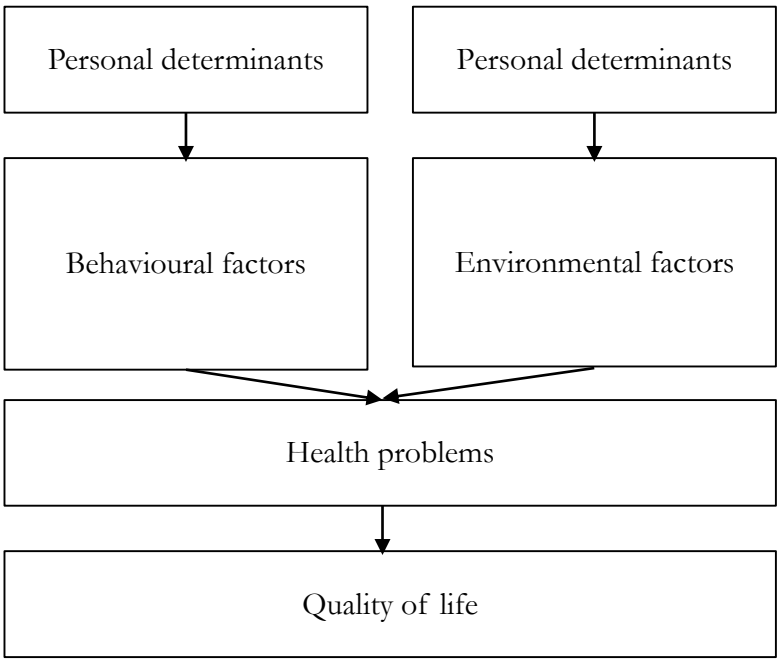

Figure 7.4 Logic model of the problem

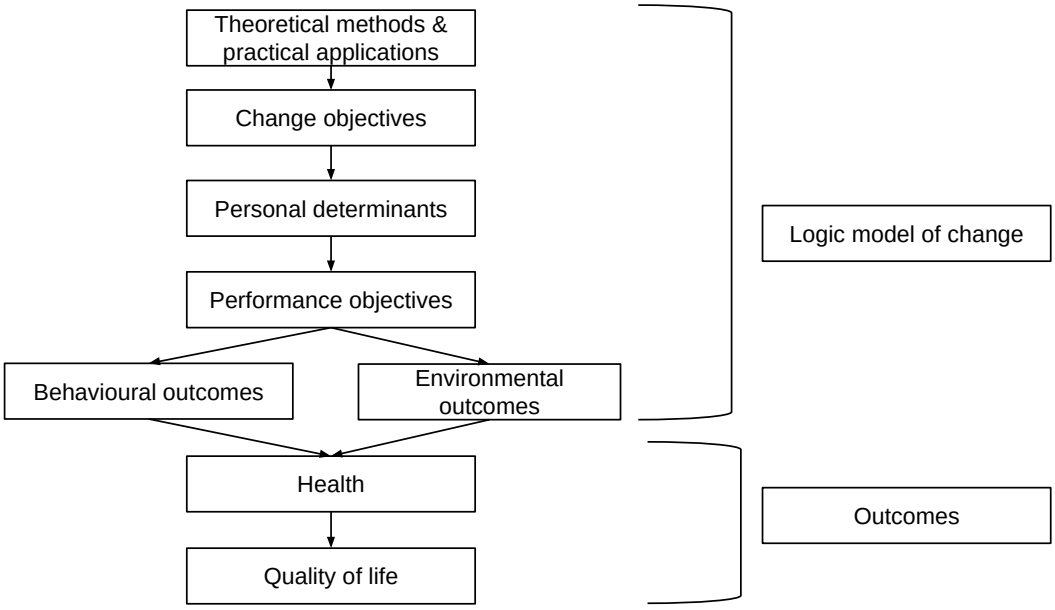

Figure 7.5 Logic model of change

7.6.3 Assessment of detailed fit and planning of adaptations (Step 3)

This step aimed to examine the fit between the logic model of behaviour change for endometrial cancer survivors and the selected program and evaluate the fit of the determinants and the theoretical methods of the original program for the new setting. Additionally, it aimed to assess the design, delivery and cultural fit, consider its implementation fit, and derive the essential elements of the original program that should be retained.

The behavioural change techniques used in the original Shape-Up were retrospectively coded using the behaviour change technique taxonomy v1 (BCTTv1) (Michie et al., 2013). The retrospective assessment also included defining the components of the logic of model change and formulation of the matrices of change objectives for the original program. This was an essential step towards improving the reporting of the intervention (Hoffmann et al., 2014).

The content update was based on (i) current guidelines for cancer survivors, and (ii) the current evidence on healthy eating and physical activity rather than weight management. Reasons for the latter change have been discussed in the introduction. A formal literature search for this update was not performed. The proposed changes included a summary of the author's work and knowledge based on reading the nutrition and physical activity literature. Justification for the changes is provided in the results section. For the refinement of the recommendations about pre-packaged bread, the Australian glycaemic index database (USyd, 2013) and UK supermarket websites were searched regarding fibre, type of flour, and glycaemic index for various bread types. The information on energy, sodium, sugar, fibre and saturated fat content of various snacks was sourced by the US (USDA, 2014) and UK (McCance and Widdowson, 2010) food composition databases. For the

illustration of resistance exercises, four cancer survivors participated as models for the photo shoot after giving signed informed consent. Participants' selection aimed to represent a range of weight categories, age groups, ethnicities, and cancer types. Lastly, the references to cookbooks in the resources section were updated with current free e-books and books available in mainstream bookstores.

In order to judge the delivery, design, and cultural fit, 15 of the 16 participants from the qualitative study received the booklet and an audio-recorded telephone interview was arranged approximately one week later. The interviews lasted approximately 15-minutes and followed the semi-structured guide adapted from (Krueger, 1997) and shown in **Error! Reference source not found.**. Participants were prompted to keep the "Shape-Up" manual if they thought it would be useful or, otherwise, return it in a pre-paid envelope. Transcription of the interviews followed the procedures detailed in Chapter 6. Data were analysed using thematic analysis (Braun and Clarke, 2006). A coding framework (**Error! Reference source not found.**) was devised by coding the first four interviews using an inductive approach. Code lists were inserted into NVivo version 10 (QSR International Pty Ltd, 2014) and the rest of the transcripts were coded. Individual suggestions for improvements in the manual were divided in two groups (content-specific and format-specific). Because each participant had different suggestions, all suggestions were reported to maximise the acceptability of the manual by cancer survivors.

The implementation fit was judged based on the delivery method and the practice-tested evaluation of the original program. Furthermore, the program was presented at the National Cancer Research Institute (NCRI) Gynaecological Cancer Cervix/Vulva and Endometrium Workshop in 2014. It was also discussed with Jill Scott, a dietitian and Macmillan Associate Learning and Development Manager, working on developing cancer-related nutrition resources for health care professionals.

Given the lack of qualitative research and formal evaluation of change objectives in the original program, identification of the essential elements was based on both feedback from the practice-tested evaluation of the "Shape-Up" in the community (ACE, 2013) and consideration of the evidence from systematic reviews and guidelines on behaviour change (Michie et al., 2009, French et al., 2011, Cavill and Ells, 2010, NICE, 2014b).

7.6.4 Adaptation of materials and activities (Step 4)

The fourth step included the preparation of the new design documents, pretesting of the adapted materials, and production of the final versions. The drafted documents were prepared in collaboration with another PhD student (Sonia Lopes) and were extensively and critically reviewed in an iterative process by team members (Rebecca Beeken, Helen Croker, Jane Wardle) ensuring that they resemble appropriately the matrices of change objectives. Due to time constraints, however, the originally planned pretesting of the materials was not possible.

7.6.5 Planning of implementation (Step 5)

In the fifth step, implementers, implementation behaviours, and outcomes were specified. The scope, sequence, and instructions of the implementation and maintenance were developed. The matrices for change objectives for implementers were retrospectively created based on the original facilitator's manual and were matched to SCT and CT constructs. These followed the rationale of the matrices in Step 3. A modified version of the original facilitator's manual was created to reflect the content changes in the adapted version. Rebecca Beeken reviewed the new version for quality assurance. These were followed by planning training and motivation activities for implementers, and logistics planning.

7.6.6 Planning of evaluation (Step 6)

The final step contained the development of the evaluation questions, selection of indicators and measures, selection of the evaluation design, and planning of the collection, analysis, and reporting of the data. This step is described in the next chapter.

7.7 Results

7.7.1 Needs assessment, organisational capacity, and logic models (Step 1)

7.7.1.1 Describe organisational capacities and goals (1A)

UCL initiated the programme planning focused on developing a healthy eating and physical activity intervention for endometrial cancer survivors to improve their overall quality of life. To do so, it collaborated with the charity Weight Concern and the final team involved a nutrition research student (myself), a health psychology student (Sonia Lopes), a health psychologist (Dr Rebecca Beeken), two academic nurses (Dr Anne Lanceley, Prof Tish Knobf) working with cancer survivors and a dietitian from Weight Concern (Dr Helen Croker). Advice from a specialist dietitian was also sought (Kassandra Montanheiro).

7.7.1.2 Conduct a needs assessment to describe the health/behaviour problems and develop a logic model of the problem (1B)

The high risk of morbidity and mortality in endometrial cancer survivors and their impaired HRQoL have been previously discussed (Chapter 1). As described in Chapter 3 and Chapter 4, obesity is negatively associated with HRQoL in this population and may be associated with lower overall survival in the long term. Results from the cross-sectional study (Chapter 5) further highlighted their suboptimal eating and physical activity behaviours. The qualitative study suggested that they highly desire information in person

regarding specific late-treatment effects and advice on healthy eating and physical activity post-treatment (Chapter 6). All constructs of SCT (i.e. outcome expectations, knowledge, self-efficacy, goals) were included in the model as determinants of healthy eating and physical activity, as a comprehensive use of theory is associated with intervention effectiveness as discussed in the introduction. Based on the above, the logic model of the problem was constructed (Figure 7.6).

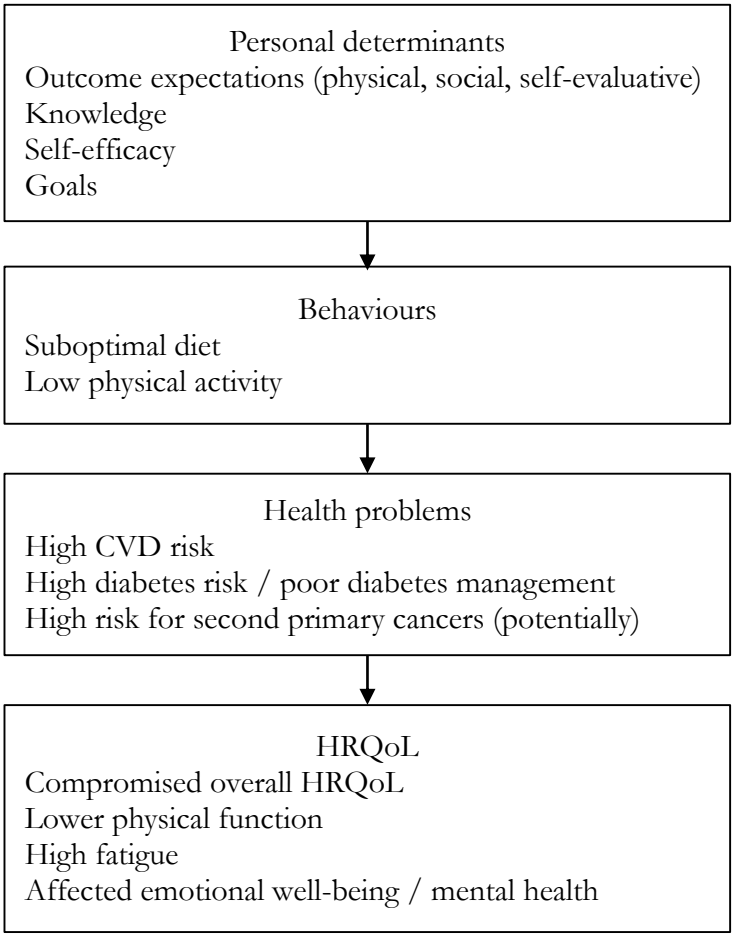

Figure 7.6 Logic model of the problem in this population

7.7.1.3 Develop a logic model of change (1C)

In this step, the logic models of changes for both the original and the adapted programs were developed. The main difference between the two was the removal of weight loss in the latter model but for the rest the model was similar. The adapted model is presented in Figure 7.8.

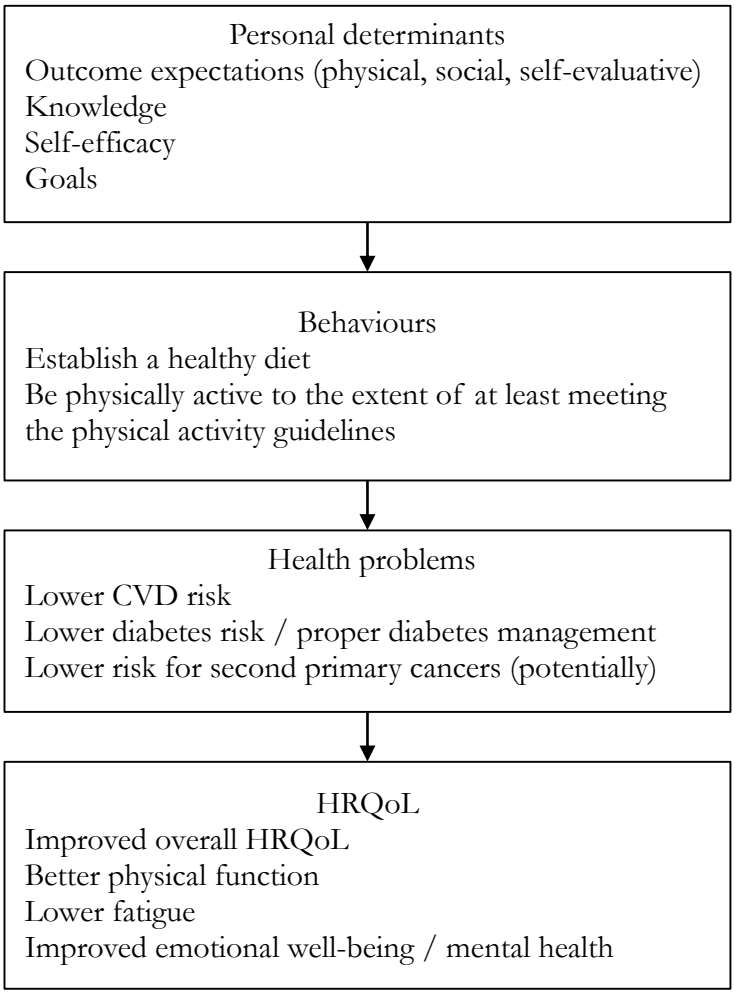

Figure 7.8 Logic model of change in endometrial cancer survivors

7.7.1.4 Write program goals (1D)

Given the above, the goal of the programme was to produce small clinically significant improvements in the overall HRQoL of participants in the first six months of program implementation (Cocks et al., 2012).

7.7.2 Search for evidence-based interventions (EBIs) (Step 2)

7.7.2.1 Search for EBIs to address the health problem/ risk behaviour/ environmental factor (2A)

A brief Internet and PubMed search for available self-help materials on nutrition and physical activity in cancer survivors did not yield sufficient results. They were mostly of informational nature (ACS, 2012), targeting specifically breast cancer survivors (Vallance and Courneya, 2008), or focused either only on diet or physical activity (AICR, 2007). A booklet produced by WCRF provided helpful lifestyle advice to cancer survivors but had only brief focus on behaviour change (Freeman, 2011).

Search on databases of effective interventions of healthy eating and physical activity for cancer survivors did not return any relevant intervention. Of the 45 potential programs identified in the NCI database, seven incorporated components of both healthy eating and physical activity. These together with the three programs identified in the Center's TRT database were evaluated further. None of them were deemed to have a good fit with the needs assessment. Reasons included intervention delivery methods (e.g. telephone), intensity (e.g. very high), and lack of long-term follow-up among others, as detailed in **Error! Reference source not found.**. Furthermore, none of them were UK based.

As discussed in the previous chapter, only a handful of various interventions aimed to improve diet and physical activity in cancer survivors have targeted endometrial cancer

survivors. The majority of them were conducted in USA, Canada, or Australia. Similarities in effectiveness of programs delivered across developed countries are expected. However, both the health systems and the causes of sub-optimal health behaviours differ between the USA and the United Kingdom (Millward, 2013). Despite the common focus of such programs on healthy eating and physical activity, these differences might make a program developed in one context less applicable in the other.

In the UK, four feasibility trials have targeted breast and colorectal cancer survivors. These have demonstrated promising results for behaviour change and both psychological and physiological outcomes immediately post-intervention but none included any long-term evaluation. One of them was evaluated in a small single-arm design (Anderson et al., 2010) while two others did not have any in person contact (Grimmett et al., 2014, O'Neill et al., 2015). The last one was particularly resource intensive (72 supervised exercise sessions, one-to-one personalised dietary advice, and 24 nutrition education seminars over 24 weeks) which might render its wider dissemination challenging (Saxton et al., 2014).

A need existed, therefore, to develop an effective behaviour change intervention for endometrial cancer survivors that can be implemented in the cancer care pathway both in terms of length of programme and resource use. As discussed in Chapter 6, the correlates of behaviour seem similar between endometrial cancer survivors and the general population. Pre-existing programmes for improving diet and physical activity in the general population, which have demonstrated usability within the National Health Service (NHS), may be an untapped resource. These programmes could be adapted to take into account the specific needs and experiences of endometrial cancer survivors while retaining the core components that have made them effective in other populations. They also have high potential for effective adoption, implementation, and sustainability.

The retrospective search confirmed that "Shape-Up" could be the ideal candidate program for evaluation. This is an eight-week weight management programme developed by the charity Weight Concern (Wardle et al., 2013). It is based on Social Cognitive Theory (Bandura, 2004) and Control Theory (Carver and Scheier, 1982). A version of this program has been favourably evaluated in terms of acceptability, physical, and psychological outcomes over 1-year follow-up (Rapoport et al., 2000).

7.7.2.2 Judge basic fit to health problem, behaviour, priority population, and organizational capacity (2B)

"Shape-Up" focuses on establishing a healthy diet and increasing physical activity through self-control, self-efficacy, and behavioural relapse prevention. It uses a non-dieting approach without focus on weight loss, and aims to achieve modest weight loss and reduction of weight regain risk through the adoption of healthy lifestyle practices. Therefore, the targeted behaviours (establishing a healthy diet and increasing physical activity to the extent of at least meeting the physical activity guidelines) were the same between the general population and endometrial cancer survivors. Additionally, the organisational capacity could support the program, given that the intervention did not require specific equipment or space but could be run in places such as community centres or churches. Finally, its acceptability based on the initial thoughts of the participants was high but this was further explored through the telephone interviews detailed in the next section.

7.7.3 Assess (detailed) fit and plan adaptations (Step 3)

7.7.3.1 Judge behavioural and environmental fit and list adaptations (3A)

The original "Shape-Up" manual was developed to reflect "The eatwell plate" recommendations, and the amended version for cancer survivors aimed to deliver similar messages regarding the balance of food groups in a person's diet. Therefore, the amendments in the "Shape-Up" manual were not major but reflected the updated evidence about healthy dietary choices and physical activity in tailored messages for cancer survivors. The only major change was the shift of focus from weight loss to healthy eating and physical activity, given the lack of strong evidence for the benefits of intentional weight loss in cancer survival outcomes presented above. Moreover, another aim was to minimise psychosocial costs associated with focusing on weight, as suggested by survivors' feedback (Section 7.7.3.3.1), and given the psychological frailty of some cancer survivors. Nationally representative data suggest that overweight or obese adults over 50 years old who lose weight may be at increased risk of depression (Jackson et al., 2014b). Thus, prevention of weight gain was the core aim of the programme regarding weight. It was acknowledged that healthier dietary and physical activity changes may induce weight loss even when weight loss is not the goal, especially in obese people. However, it was expected that this weight change might be minimal and much lower than the clinically relevant 5-7% weight loss (Hartmann-Boyce et al., 2014), especially as overall dietary restriction was not encouraged. Details on specific changes on the manual content are presented below.

7.7.3.1.1 Introduction

The introductory section remained widely the same with small changes emphasising the importance of healthy lifestyle towards the improvement of overall quality of life and long-

term symptoms, such as fatigue, while acknowledging the difficulty of behaviour change given the symptoms and side effects burden.

7.7.3.1.2 Section 1: Getting ready to Shape-Up

While the manual targeted cancer survivors with stable health, it emphasised that the healthcare team needs to approve participation in the program and be kept updated of any weight changes more than 5% in less than six months. This reflected the internationally agreed definition of cancer cachexia (Fearon et al., 2011).

7.7.3.1.3 Section 2: The Shape-Up Healthy Eating Plan

As stated, the "Shape-Up following cancer treatment" manual was in line with the recommendations of "The eatwell plate." Following the above recommendations and recent evidence (Katz and Meller, 2014), specific emphasis was given to the promotion of a plant-based diet based on whole fruits and vegetables, whole grains, beans, and nuts, while limiting the amount of saturated fats, processed foods, salt, added sugars, and refined grains. Michael Pollan's statement "Eat food, not too much, mostly plants" (Pollan, 2009) was added for simply summing up the evidence regarding healthy eating (Katz and Meller, 2014). The interviewed cancer survivors also indicated the usefulness of simple messages.

There is a current debate (Wells, 2013, Ludwig and Friedman, 2014) about the relevant importance of diet quality (Walsh et al., 2013) compared to the thermodynamic principle of a calorie is a calorie (food quantity) (Hall et al., 2011) for successful weight management and overall health. Until long-term trials focusing on the mechanisms of obesity sufficiently address this chicken or egg debate, the programme incorporated both portion control (for weight maintenance) and dietary quality advice. Therefore, the food portion advice was based on the standard 2,000kcal diet for women, rather than the 1,500kcal in the original program.

7.7.3.1.4 Carbohydrates

Regarding carbohydrates, the focus remained on education about low-glycaemic index foods, as this is in accordance with the plant based diet and has shown large effects regarding diabetes prevention (Ley et al., 2014). Considering simplicity and the lack of glycaemic index in food labels, the term "low-glycaemic index" was approximately reflected by "high-fibre foods".

Regarding starchy products, emphasis was given to the selection of whole grain varieties. However, implementation of this advice may be quite challenging due to the multiple definitions of whole grains (Seal et al., 2006) that can limit the ability of consumers to select wholegrain foods that are of low glycaemic index, with high fibre content and have limited amounts of added sugars and salt. A US analysis revealed that among five criteria of defining whole grain products, products with a ratio of total carbohydrate to fibre of less than 10:1 (10:1 ratio) were the healthiest and a lower ratio of 5:1 identified even healthier products in terms of energy, fibre, sugar, sodium, and *trans*-fat content (Mozaffarian et al., 2013). In terms of UK pre-packaged breads, this criterion applied only to the granary wholemeal or seeded wholemeal breads, which were also meeting the low glycaemic index criterion (Henry et al., 2007). Therefore, although limited in the market, these products were promoted as wholegrain breads in the carbohydrates section. Further advice was added regarding the potential bowel effects from a high-fibre diet, and alternatives, such as mixed white and brown bread, were proposed.

7.7.3.1.5 Eggs and food safety

Egg-specific food safety recommendations were also included (NHS, 2013). A general food safety section has also been added following the ACS Guidelines (Rock et al., 2012).

7.7.3.1.6 Processed foods and low-fat choices

Compared to the 2013 "Shape-Up" edition, the focus on selection of processed foods shifted from low-fat, low-calorie choices towards choices low in saturated fat, added sugars, salt and high in fibre. This reflects the current evidence suggesting that overall fat intake is not associated with higher risk for CHD (Oh et al., 2005) or stroke (He et al., 2003, Larsson et al., 2012), despite decreasing trends in overall fat intake and promotion of low-fat choices in cardiovascular disease prevention guidelines (Lichtenstein et al., 2006). These observations were confirmed by randomised trials (Howard et al., 2006, Estruch et al., 2013). Instead, research strongly supports that *trans*- and saturated fatty acids promote CVD risk, whereas monounsaturated and polyunsaturated fatty acids lower it (Mente et al., 2009). Furthermore, this reflects the current guidance of the WHO and the SACN about free sugars consumption (less than 5% of energy intake) (WHO, 2014, SACN, 2014) and the evidence regarding salt intake and CVD risk (Strazzullo et al., 2009).

In light of the inherent limitations of food package labelling (Scarborough and Rayner, 2014) and with the aim to promote nutrient-dense but low energy-dense foods, the importance of the sodium, sugar, fibre and saturated fat amount per 100g of processed foods was stressed rather than their amounts per portion size. The initial idea of comparing the energy, sodium, sugar, fibre and saturated fat content of healthier foods (e.g. nuts and fruits) to less healthy choices (e.g. crisps and bars) was not followed. Instead, the booklet provided only a breakdown of the content of these nutrients together for the unhealthy sweet and savoury snacks. The reason for providing data only for processed foods was that healthier foods, like nuts, scored high in the saturated fat content per 100g, while some fruits scored low in fibre and high in sugar per 100g. This was an expected consequence since not all nutrients are naturally occurring in all foods and that the synergy of the nutrients in the whole foods may be important in fostering disease prevention (Jacobs and

Tapsell, 2013, Estruch et al., 2013). Therefore, whole foods were promoted in this section compared to processed snacks, but the labelling of the above nutrients was emphasized when choosing processed foods. *Trans*-fats were not included because they have been generally eliminated from the food chain and the UK population intake of *trans*-fat is below the upper recommended level (PHE, 2014).

7.7.3.1.7 Healthy but affordable food choices

Providing healthy lifestyle recommendations in disadvantaged groups, who are probably the most in need (Drewnowski and Darmon, 2005), is challenging. Among others, high cost of healthy foods is a significant barrier (Malik et al., 2013, Jones et al., 2014). This was also reported in the qualitative interviews. Even irrespective of their educational level, higher income adults seem to eat more fresh fruits and vegetables (Lallukka et al., 2010). Hence, in order to meet their caloric needs and avoid starvation, people in the most disadvantaged groups may be forced to consume cheaper food, evident by the overwhelming turn for assistance at food banks (TrussellTrust, 2014). Cheaper food is generally of low nutritional value (high in sugars, fats, and salt while low in fibre) and less satiating. Thus, advice for using shopping lists, weekly meal planning (DoH, 2011), cooking, preference for frozen plant foods, and for choosing nutrient-dense snacks aimed at targeting affordable, healthy, and tasty foods.

7.7.3.1.8 Supplements, superfoods, and organic food

The advice regarding supplements and organic food followed that of the aforementioned guidelines (Rock et al., 2012). While the Dietary Guidelines for Americans recommend a B12 supplement for the elderly due to malabsorption (USDA, 2010), no recommendations exist in the UK. Vitamin B12 deficiency might be prevalent especially in the elderly cancer

survivors who receive bowel radiation. Supplement advice was left to the discretion of the health care professionals.

Regarding organic foods, the advice was neutral, given the same vitamin content of both organic and conventional food but higher concentration of pesticides and antibiotic-resistant bacteria in the latter (Smith-Spangler et al., 2012). Particular emphasis was given in washing all fruits and vegetables well in order to remove pesticide residues (Keikotlhaile et al., 2010).

7.7.3.1.9 Section 3: Getting active

The physical activity section followed the current recommendations for cancer survivors (Mishra et al., 2012, Schmitz et al., 2010). Emphasis was added on the link between physical activity and various cancers as well as the benefits of physical activity after cancer treatment, as discussed in Chapter 2 and 0. Cancer late-effects, including lymphoedema, anaemia, fatigue, and diarrhoea, were added to the questionnaire assessing the safety of engaging with physical activity. Swelling was also added to the contra-indications for continuing to exercise.

The previous version of "Shape-Up" primarily focused on promotion of aerobic activity. Alongside aerobic activity, resistance exercise is relatively safe (Cormie et al., 2013b, Cormie et al., 2013a). It can also yield important benefits for cancer survivors, such as preservation of bone mineral density and increased bone-free lean mass (Winters-Stone et al., 2011) that may reduce risk of falls. Longitudinal data also suggest that resistance training is associated with lower all-cause mortality in cancer survivors (Hardee et al., 2014). Multiple biological mechanisms may be in place including stimulation of the anabolic mammalian target of rapamycin (mTOR) pathway (Fujita et al., 2007). Therefore,

illustrative guidelines on how to do simple strength, balance, and flexibility exercises based on previous materials (NIH, 2013, NHS, 2014) were included in this section.

7.7.3.1.10 Sleep

Some cancer survivors may have disturbed sleep (Davidson et al., 2002). Furthermore, evidence from the Nurses' Health Study and the NIH-AARP Diet and Health Study suggests a positive association between sleep disturbances and obesity (Patel et al., 2006, Xiao et al., 2013). Nonetheless, the evidence is more conclusive for children and young adults rather than older adults, as some smaller and shorter studies have not significantly linked the two variables (Nielsen et al., 2011). Potential mechanisms include both increased food intake and decreased energy expenditure (Zimberg et al., 2012). Regarding the first, deregulation of appetite hormones may increase hunger. Regarding the latter, sleep deprivation may be related with higher fatigue to engage with physical activity and may decrease body temperature. Much research has been criticised based on lack of appropriate trials to draw causal inferences, further methodological pitfalls, and lack of large changes in sleep patterns in population-based data (Horne, 2011). While future trials will provide further insight, duration and quality of sleep are positively linked to overall wellbeing (Horne, 2011). Therefore, a small section on sleep hygiene was added (Harvard, 2007).

7.7.3.1.11 Resources

Following the update of the cookbooks, free mobile applications regarding diet and physical activity monitoring, such as "My Meal Mate" (Carter et al., 2013), the "British Heart Foundation Healthy Heart Recipe Finder", and applications from the "Change4Life" campaign were added to this section.

7.7.3.2 Judge determinants and change methods fit and list adaptations (3B)

The targeted behaviours, behavioural determinants, and performance objectives remained the same except the performance objective "Cut down on quantity" which was rephrased to "Keep an eye on portion sizes" with respective changes in food portion recommendations. Based on the content-specific changes detailed above, change objectives and practical applications targeting weight management were removed while those for late-treatment effects management, resistance exercises, and increase in expectations that health care professionals will approve their lifestyle changes were added. These are detailed in **Error! Reference source not found.**.

7.7.3.3 Judge delivery, design, and cultural fit and list adaptations (3C)

Fifteen participants critically reviewed the "Shape-Up" manual and made suggestions for improvement. The two major themes to emerge were about the manual and about the delivery of the intervention. Suggestions regarding the content, format, and delivery of the intervention based primarily on individual comments are available in **Error! Reference source not found.**.

7.7.3.3.1 Shape-Up manual

Most participants welcomed the booklet in its current format and 13/15 (86.7%) participants decided to keep the manual because they found it useful. However, many noted its physical volume and/or content detail as a disadvantage.

> *I thought the A5 size was very good, very portable. I like the fact that it is ring-bound, that makes it very easy to use. […] I think if it was whittled down half the size, I think that would be quite easy to carry around, to be honest. But if you wanted to do it in smaller ones, that would be all right, and then just take that to the first two*

> *weeks and then use the next one for the next two weeks. You could do that (FG1_1, 57 years, a & b & c)*[16].

> *It is really good. I like the fact that is looking at the whole life rather than the diet. […] I suppose it because it looks so big it would be a bit… You can look at it and go Oh my God that's a lot to read. That can be off-putting maybe. That is the only downside really (Int_6, 46 years, a).*

> *It is all very good, and it is beautifully set out. […] It could go on The Eve Appeal's website. But I think what's important, you know, people have a very short attention span, and I think that if you've got something really short and punchy, that would be good (Int_1, 67 years, a & b & c).*

Survivors expressed favourable opinions about various content aspects of the book, including the physical activity plan, the self-monitoring, the emotional eating, and the reasoning for making changes.

> *I love the fact it is in stages, the fact that it is very easy to understand, and you can evaluate yourself, so it becomes your own kind of workbook, really (FG2_2, 33 years, a & b & c).*

Some participants considered the nutrition section to be unnecessarily detailed as they regarded themselves to be quite familiar with the topic. They were particularly keen on tailoring the information particularly to endometrial cancer survivors.

> *I think it is really important [to tailor the information]. There should be more out there for people who have endometrial cancer (Int_2, 37 years, a).*

[16] a: surgery; b: surgery & radiation; c: surgery & radiation & chemotherapy

> *To have something like that which is targeted very specifically to people in our situation is a good thing, and I like the idea of doing a programme, with an exercise programme alongside it, which again is tailored to people in our situation (FG1_5, 60 years, a & b & c).*
>
> *Well, to be totally frank, I would probably see myself, if I came to this sort of group, as acting more… certainly, on the exercise bit, and just saying, 'Well, I can manage this much at my age.' But perhaps I'm a bit atypical. I would not be happy to take on ideas, 'Oh, you should do something more energetic,' you know? (FG2_1, 80 years, a).*

Therefore, recommendations on management of fatigue and bowel issues were added to the booklet. Furthermore, Motivational text from the qualitative study and other qualitative studies [17] with cancer survivors conducted by our research group was extracted in collaboration with Sonia Lopes. These were incorporated in the manual. Cancer-specific resources were added at the end of the manual, including the ACS and CRUK websites, the Macmillan Cancer Support webpages. Reference to a book with information and recipes regarding nutrition-associated, cancer specific symptoms and treatment effects has also been added (NCI, 2011).

7.7.3.3.2 The endometrial cancer survivors bolt-on section

Given the overall currently limited tailored information for cancer survivors (Williams et al., 2015b), a section specific to endometrial cancer survivors was developed. It comprised a one-page sheet with information about statistics for endometrial cancer survival and potential causal but modifiable factors of endometrial cancer, given the currently limited evidence of nutrition, diet, and physical activity after the end of cancer treatment. The

[17] In preparation for publication.

latter point was further acknowledged. However, emphasis was given for their imperative role in improving quality of life and physical function, and decreasing the risk for heart disease, the most common cause of death among endometrial cancer survivors (Ward et al., 2012).

7.7.3.3.3 Shape-Up delivery

Some participants were happy with the proposed eight weekly sessions while others recommended them monthly. Proximity and a busy schedule were identified as potential barriers.

> *Six to eight weeks sounds about right (Int_3, 64 years, a & c).*
>
> *I could see that would be, sort of, a chapter by chapter approach almost. I could find that quite difficult to keep to, because we do various things. Obviously, the sensible thing to do would be to have a certain day and try to stick to that. But for me, personally, that could be hard. Obviously, I try […] I would find it quite hard, even if it would stretch for longer, to always be available (FG2_1, 80 years, a).*

The opinions about the inclusion of cooking classes in the program were mixed. Some of them liked the idea mostly because this would be an enjoyable activity rather than because they did not possess good cooking skills. Indeed, good cooking skills was the reason that others disagreed with the idea. All of them endorsed exchange of recipes instead.

> *It is difficult for me to say [if I would like cooking class to be part of the programme] because I am an obsessive cook anyway (laughing). I love cooking I am not sure I would... If people can come up with really good ways of making delicious food that isn't high in fat or sugar, that's great. I think for me personally probably not. Well, that could be fun, I suppose as part of an 8-week session, one week might be fun to have that (Int_3, 64 years, a & c).*

> *Yes, definitely. That [cooking classes] would be great. If anybody else within this group has any ideas about recipes or anything like that was proven to work for them; that would be good (Int_2, 37 years, a).*

Many survivors preferred the group to be delivered by another cancer survivor who would be further ahead in her cancer pathway, have done the program and who could provide them with her own experience and reassure them. Others felt that the facilitator should be a health care professional, such as a dietician or a nurse who would work alongside another professional such as a psychologist or physiotherapist. One woman spontaneously suggested the current delivery format of the Shape-Up, being a self-help group where the participants rotate each week as facilitators.

> *I think there is nothing more powerful than somebody who is a living example of how such a programme can help. And it's really important to have somebody who can speak from personal experience. I do not think there's any point in having a nurse or a doctor or whatever, you know. I do not think there's any point in having anybody like that (Int_1, 67 years, a & b & c).*

> *Personally, I think we have these once a week meet ups. If it is for a limited number of weeks, people can commit to that, but if it any longer, then people wouldn't do it. Personally, I don't think you can have one person to run them all the time. It is got to be democratically decided, the last week for the next week or something. But obviously it is a discussion group for everybody. Somebody has to take the role off (FG1_5, 60 years, a & b & c).*

> *Somebody with some medical knowledge. I mean a nurse, practice nurse (FG1_3, 55 years, a & c).*

The majority of participants agreed that group sessions would be more helpful and motivating for being physical active than exercising alone. Some of them thought that bringing a friend to the group would be motivating. One participant preferred the delivery to be a one-to-one, individual self-help program rather than group-based. Another informant preferred it in a group of people from the general population rather than with other cancer survivors to avoid potential anxiety caused by interacting with other cancer survivors.

> *In groups. One-to-one, in groups, whatever it is. Face to face. Some sort of contact (Int_5, 53 years, a).*

> *I would say doing things in a group is easier always than doing them individually (FG1_5, 60 years, a & b & c).*

Based on this feedback, it was decided to keep the original delivery of the program unchanged. The intervention would be delivered in-group sessions for eight weeks given the high preference of endometrial cancer survivors for face-to-face contact with the intervention facilitator. Keeping the duration and frequency of the program on eight weekly meetings aimed to balance the lack of agreement among survivors for the optimal duration and frequency of the programme delivery.

7.7.3.4 Judge implementation fit and list adaptations (3D)

A version of "Shape-Up" for the general population is currently used in North Essex through the NHS. Its most recent practice-tested evaluation demonstrated positive results in adoption of health behaviours and successful modest weight loss, with 96% of 422 respondents recommending it as a weight management programme. For example, 93% reported establishing a regular eating pattern, 92% setting effective lifestyle goals and working towards them, 95% feeling more in control of their eating habits, 89% increasing

physical activity, and 90% being better able to manage 'triggers' that may lead to unhealthy behaviours (ACE, 2013). The program is also being run in the borough of Camden – part of the population pool for the current intervention – as part of the local Joint strategic needs assessment (Camden, 2013).

It was considered that the implementation fit would be adequate given the conservation of the initial delivery method. Nonetheless, this is a very specific segment of the population widely dispersed across the county. Thus, program implementation might be more challenging in local centres, such as community centres, whereas treatment hospitals, Macmillan Cancer Support Centres, and Maggie Centres might serve this purpose well.

Furthermore, clinicians and researchers participating in the NCRI gynaecological cancer workshop were supportive of the program, indicating its future potential acceptability. The dietitian, who might represent potential program implementers, was familiar with the original program and supportive of it. Additionally, the intervention is in accordance with the National Cancer Survivorship Initiative, which envisages a sustainable personalised lifestyle support for cancer survivors with them playing an active part in the decision-making (DoH, 2010).

7.7.3.5 Identify essential elements of the selected intervention and how to retain them (3E)

Based on the intensity of the BCTs used, the essential ones included self-monitoring of behaviour, behavioural goal setting, self-incentives, and problem solving. The differences in the BCTs between the original and adapted versions are summarised in Table 7.1. These differences primarily reflected the weight loss component and were not considered essential elements of the program based on the results of the practice-tested evaluation that highlighted the focus on feedback regarding behaviour changes over weight monitoring

(ACE, 2013). This indicated that the step-by-step approach was comprehensively addressing behaviour modification. The three added BCTs were demonstration of behaviour for the resistance exercises, conservation of mental resources, which was a refinement of an existing program component, and credible source for making it relevant to the targeted population.

It could be argued that the combination of BCTs made the program effective rather than specific essential ones. Furthermore, all BCTs identified in the literature and coded against the BCTTv1 were included in both the original and adapted versions of the program. Therefore, the theoretical methods of the program remained largely unchanged. The adapted matrices for change objectives for diet and physical activity are shown in Table 7.2 and Table 7.3, respectively.

Table 7.1 Behaviour change techniques (BCTs) in the original and adapted versions of the "Shape-Up" and effective BCTs from the literature

		Behaviours in original Shape-Up		Behaviours in Shape-Up following cancer treatment		BCTs identified from the literature to facilitate health behaviour changes		
Category	BCT	Establish a healthy diet	Increase physical activity to the extent of at least meeting the PA guidelines	Establish a healthy diet	Increase physical activity to the extent of at least meeting the PA guidelines	Systematic reviews (Michie et al., 2009, French et al., 2011)	NOO Guidelines (Cavill and Ells, 2010)	NICE guidelines (NICE, 2014b)
Goals and planning	Behavioural goal setting	☒	☒	☒	☒	☒	☒	☒
	Problem solving	☒	☒	☒	☒	☒	☒	☒
	Action planning	☒	☒	☒	☒	☒		
	Review behavioural goals	☒	☒	☒	☒			
	Discrepancy between current behaviour and goal	☒	☒	☒	☒			
	Goal setting (outcome)	☒	☒					
Feedback and monitoring	Self-monitoring of behaviour	☒	☒	☒	☒	☒	☒	☒
	Self-monitoring of outcome of	☒	☒					

		Behaviours in original Shape-Up		Behaviours in Shape-Up following cancer treatment		BCTs identified from the literature to facilitate health behaviour changes		
	behaviour							
	Feedback on behaviour	☒	☒	☒	☒	☒	☒	☒
	Feedback on outcome of behaviour	☒	☒					
Social support	Social support (unspecified)	☒	☒	☒	☒	☒	☒	☒
Shaping knowledge	Instructions on how to perform behaviour	☒	☒	☒	☒			☒
Natural consequences	Information about health consequences	☒	☒	☒	☒	☒		
	Information about emotional consequences		☒		☒	☒		
Comparison of behaviour	Demonstration of behaviour				☒			☒
	Facilitate social comparison					☒		
	Information about others' approval	☒	☒	☒	☒			

		Behaviours in original Shape-Up		Behaviours in Shape-Up following cancer treatment		BCTs identified from the literature to facilitate health behaviour changes
Associations	Satiation	☒				
Repetition and substitution	Behavioural practice	☒		☒		
	Behaviour substitution	☒	☒	☒	☒	☒
	Habit formation	☒	☒	☒	☒	
	Graded tasks	☒	☒	☒	☒	
Comparison of outcomes	Credible source			☒	☒	
	Pros and cons	☒	☒	☒	☒	
Reward and threat	Social reward	☒	☒	☒	☒	
	Self-incentive	☒	☒	☒	☒	☒
	Non-specific incentive	☒	☒	☒	☒	
Regulation	Reduce negative emotions	☒	☒	☒	☒	
	Conserving mental resources			☒		
Antecedents	Reducing exposure to cues for the behaviour	☒	☒	☒	☒	☒

		Behaviours in original Shape-Up		Behaviours in Shape-Up following cancer treatment		BCTs identified from the literature to facilitate health behaviour changes
	Distraction	☒	☒	☒	☒	☒
	Information about antecedents	☒	☒	☒	☒	
Identity	Framing / reframing	☒	☒	☒	☒	☒
Self-belief	Verbal persuasion about capabilities	☒	☒	☒	☒	
	Self-talk	☒	☒	☒	☒	
Non-categorised	Time management					☒
	Use of follow-up prompts					☒
	Assertiveness					☒

BCTs in red indicate those removed from the original Shape-Up while those in green indicate additions in the adapted version. All BCTs are based on the BCTTv1 taxonomy apart from the non-categorised that are based on the CALO-RE taxonomy. NOO: National Obesity Observatory.

Table 7.2 Matrix for change objectives aiming at establishing a healthy diet[18]

Performance objectives	**Behavioural determinants Outcome expectations (physical, social, self-evaluative)**	**Knowledge**	**Self-efficacy**	**Goals**
PO 1. Have a regular eating pattern	OE 1.1. Identify their current eating pattern **Feedback on behaviour (CT)** From a list of 7 different eating patterns, the person picks the one that applies to them and reads feedback based on their choices	KN 1.1. Recognise the benefits of regular eating and breakfast **Information about health consequences (SCT)** Verbal and written explanation that regular eating can regulate hunger and that breakfast can improve cardiometabolic risk	SE 1.1. Express confidence in their ability to start following a regular eating pattern and eating breakfast regularly **Habit formation (SCT)** Be prompted to start eating at the same time each day SE 1.2. Express confidence in eating regularly **Problem solving and social support (unspecified) (SCT)** Identify barriers to eating regularly during the previous week Generate strategies (as a group)	GO 1.1. Be prompted to increase the difficulty of their goals slowly until behaviour is performed **Graded tasks (SCT)** Be prompted to make behavioural changes in the following order • Changes towards PO 1 • Changes towards PO 2 • Changes towards PO 3 GO 1.2. Set a regular eating goal **Behavioural goal setting (SCT)** Set a SMART regular eating goal based on GO 4.1.

[18] Determinant-specific change objectives target each performance objective. The nested tables refer to the behaviour change techniques (BCTs) in bold text, their link with the theory in brackets, and their practical application in non-bold text. The BCTs and practical applications with no fill are present only in the booklet; those with light blue are present both in the booklet and the sessions; and those with dark blue only in sessions. The same notes apply for Table 7.3.

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			to overcome barriers and increase facilitators to regular eating	
PO 2. Adhere to the Eatwell plate principles	OE 2.1. Recognise the value of the behavioural recommendations **Framing / reframing (CT)** Identify the difference between a fad diet and learning how to carry on with the healthy lifestyle for a lifetime OE 2.2. Review their shopping pattern **Feedback on behaviour (CT)** From a list of 7 different shopping patterns, the person picks the one that applies to them and reads feedback based on their choices OE 2.3. Be aware that others also face difficulties following a healthy	KN 2.1. Understand components of each food group and their benefits and risks **Information about health consequences (SCT)** Explanation of the health benefits (vegetables, fruits, whole grains, pulses, healthy oils) and risks of the various food groups (foods/drinks high in fat/sugar, saturated and trans fats, refined grains, red meat, excessive alcohol intake) Recognise the principles of Eatwell plate, the five food groups and their ideal proportions Recognise the different names of sugar and fat on food labels Understand the risks and benefits of supplements	SE 2.1. Express confidence in choosing healthy foods and drinks **Instructions on how to perform the behaviour (SCT)** Recognise ways of eating enough fruits, vegetables and whole grains; making healthy choices from the protein & dairy groups; eating less fatty and sugary foods; and cutting down alcohol Recognise ways of cutting down on sugary drinks Recognise ways of having healthier lunches Recognise which snack to choose Identify foods to store in the cupboard / fridge / freezer List ways that eating out can fit into the new eating plan	GO 2.1. Set a healthy eating goal **Behavioural goal setting (SCT)** Set one or more SMART goal on eating a balanced diet based on GO 4.1.

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	diet after cancer treatment and increase motivation to be more active **Information about others' approval (SCT)** Read motivational quotes from other cancer survivors about healthy eating OE 2.3. Increase expectation that health care professionals will approve their lifestyle changes **Credible source (SCT)** Read information from nurses in favour of healthy eating		Recognise healthy and unhealthy options in various types of restaurants Recognise healthy options in ready meals Recognise ways of having an affordable healthy diet Consult when necessary suggested cookbooks **Behavioural practice / rehearsal (SCT)** Practice matching various foods under each food group SE 2.2. Express confidence in maintaining a balanced diet in the presence of bowel symptoms **Instructions on how to perform the behaviour (SCT)** Recognise ways of maintaining a balanced diet in the presence of bowel symptoms	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			SE 2.3. Express confidence in food safety **Instructions on how to perform the behaviour (SCT)** Recognise ways of avoiding risk for food born-illnesses SE 2.4. Express confidence in adhering to the eatwell plate when eating out **Conserving mental resources (SCT)** Be prompted to carry wallet-size cards with healthy and unhealthy options in various types of restaurants SE 2.5. Express confidence in understanding food labels **Behavioural practice/rehearsal (SCT)** Examine the ingredients list Compare nutritional values of various sweet and savoury snacks Compare different product labels	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			to the guidelines and to the guide to good shopping Examine the sugar, fat, and calorie content per 100g, compare it to guidelines, and decide if the foods are healthy options Interpret nutritional claims correctly	
PO 3. Keep an eye on portion sizes	OE 3.1. Recognise their aims regarding food quantity **Information about health consequences (SCT)** Written explanation that keeping an eye on portion sizes can help them avoid undesirable weight gain	KN 3.1. Understand what are the recommended amounts from each food group to avoid weight gain **Instructions on how to perform the behaviour (SCT)** Describe what constitutes a serving from each group Describe the amounts of servings aiming for from each group Observe portion sizes of various foods from all food groups	SE 3.1. Express confidence in keeping an eye on portion sizes **Behavioural practice/rehearsal (SCT)** Using the food portions, create a day's food intake aligned with the recommendations	GO 3.1. See GO 4.1
PO 4. Create and maintain a discrepancy-reducing feedback loop	OE 4.1. Express confidence in their ability to change their behaviour **Pros and cons (SCT)**	KN 4.1. Become aware of their current dietary pattern **Self-monitoring of behaviour (CT)**	SE 4.1. Express confidence in their ability to increase their willpower **Verbal (and written)**	GO 4.1. Compose an action plan towards establishing a healthy diet **Action planning and goal**

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	Explain of the components of motivation to change Review examples of advantages and disadvantages for (not) changing their lifestyle Analyse their advantages and disadvantages of (not) changing their lifestyle OE. 4.2. Recognise the importance of making one behaviour change at a time **Framing / reframing (CT)** Recognise that making one behaviour change at a time will be more advantageous in the long term compared to making too many changes at once OE 4.3. Recognise the value of self-monitoring **Self-monitoring of behaviour (CT)** Written explanation that self-monitoring of behaviour can improve behaviour practice and	Record the time, amount and type of food and drink each day using (if preferred) the Shape-Up diary	**persuasion about capabilities (SCT)** Understand that willpower is a practicable skill (written) Understand that they can learn to swap unhealthy habits to healthy ones SE 4.2. Express confidence in setting SMART healthy eating goals **Behavioural practice (SCT)** Define the principles of SMART goal setting Practise translating vague goals to SMART ones SE 4.3. Express confidence in rewarding themselves for achieving their SMART goals **Self-incentive & non-specific incentive (SCT)** List their own potential rewards	**setting (behaviour)** Plan in detail the performance of their first SMART goal Plan things that might get in the way of achieving the goal Plan how and when they will review the goal Plan who might help them GO 4.2. Set a lifestyle target **Goal setting (outcome) (SCT)** Set a lifestyle goal (e.g. healthier life) as an outcome of changing eating and activity behaviours GO 4.3. Compare intake to personal goals and guidelines **Self-monitoring of behaviour and goal setting (behaviour) (CT)** Categorise consumed foods and drinks in servings from each food group Score their daily consumption of

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	maintenance Provision of food diaries each week Record the time, amount and type of food and drink each day using (if preferred) the Shape-Up diary Verbal re-affirmation that self-monitoring of behaviour through diaries can improve behaviour practice and maintenance at the end of the programme OE 4.5. Express confidence in (not) seeking social support **Problem solving and social support (unspecified) (SCT)** Identify helpful and unhelpful social support towards healthy eating changes (e.g. family, friends, health care professionals) Problem solve potential social impediments OE 4.6. Plan their self-reward		SE 4.5. Decide if discrepancies exist when comparing intake to personal goals and guidelines **Discrepancy between current behaviour and goal (CT)** Compare their score (SE 5.2) to personal goals or guidelines in order to draw attention to the discrepancy. SE 4.6 Maintain self-monitoring through diaries **Problem solving (SCT)** Identify as a group barriers to keeping a food and activity diary Discuss ways in which they can overcome the barriers SE 4.7. Express confidence in achieving SMART goals **Review of behavioural goals, problem solving, and social support (unspecified) (SCT)**	each food group Review their SMART goal Evaluate outcome of their SMART goal GO 4.4. Expressing confidence in maintaining monitoring, goal setting, incentivisation after the end of the programme **Action planning, goal setting (behaviour), problem solving, and self-incentive (SCT)** Plan in detail their dietary and physical activity SMART goals, identify barriers and facilitators and strategies to facilitate/overcome them, specify review date, and reward **Review behaviour goals and information about others' approval (SCT)** As a group, review each participant's goals and discuss other's views on the plan and potential modifications if goals unrealistic or participants

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	Self-incentive & non-specific incentive (SCT) Understand the value of rewards for achieving their SMART goals Brainstorm ideas for non-food incentives Plan to reward self when they review their goals if they achieve their SMART goals OE 4.7 Reward success **Social reward (SCT)** Facilitator verbally praises participants if and only if participants have progressed with their goals OE 4.8. Receive support from each other while making behavioural changes **Social support (unspecified) (SCT)** Distribute to each other their contact details so that they support each other on the		Re-examine their behaviours. Facilitator and group members provide evaluative feedback if they have (not) met the SMART criteria and if they have rewarded themselves for achieving the goal. Participants should problem-solve themselves with the help of the rest of the group ways of making their goals fit with the SMART criteria	overwhelmed

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	behavioural changes during the program Be aware that others also face difficulties following a healthy lifestyle after cancer treatment Get support and ideas from group members on following a healthy lifestyle OE 4.9. Identify potential sources of external support at the end of the programme **Social support (unspecified) (SCT)** Discuss if continuous support from other healthy lifestyle services can be helpful after the end of the programme Advice on how they can find information about support in their local area			
PO 5. Deal effectively with triggers of unhealthy eating and lapses	OE 5.1. Reframe unhelpful thoughts about lapses to helpful ones **Framing/reframing (CT)**		SE 5.1. Express confidence in dealing with external triggers **Avoidance/reducing exposure to cues for the behaviour (CT)**	GO 5.1. See GO 4.1

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	Identify five helpful and four unhelpful example thoughts about lapses from their healthy eating and physical activity plan		Be prompted to identify and try to avoid cues promoting unhealthy eating (e.g. sight or smell of food)	
	For the unhelpful thoughts, generate alternatives that are more positive and/or would help them recover from the lapse		**Distraction (CT)**	
			Be prompted to use an alternative focus for attention to avoid triggers for comfort eating	
			Problem solving (SCT)	
			Be prompted to identify the triggers for unhealthy eating and generate a strategy to overcome them (e.g. do not skip meals before going to a party to avoid overeating)	
			Analyse various example external triggers (e.g. buffet party) and select strategies (i.e. avoidance, distraction, problem solving) to overcome them	
			SE 5.2. Express confidence in dealing with cravings	
			Problem solving & distraction (SCT)	
			Identify example eating situations	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			either as hunger or craving Receive advice to eat regularly to deal with hunger and information that cravings last for only 20 minutes Generate strategies to overcome cravings (e.g. distraction) Be prompted to distract self when a craving comes SE 5.3. Express confidence in dealing with unhelpful thoughts **Problem solving (SCT)** Understand how unhelpful thoughts trigger unhealthy behaviours Identify unhelpful thoughts that trigger unhealthy eating behaviours Generate and select strategies to overcome unhelpful thoughts **Behavioural practice (SCT)** Practice translating unhelpful thoughts that might impede	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			healthy eating goals to helpful ones **Self-talk (SCT)** When experiencing an unhelpful thought, be prompted to remind themselves what they are trying to achieve and why SE 5.5. Express confidence in dealing with emotions **Problem solving (SCT)** Understand how emotions can trigger unhealthy behaviours Identify emotions that trigger unhealthy eating behaviours Generate and select strategies to overcome them **Distraction (CT)** Identify ways for distracting from the mood Be prompted to focus attention on this alternative way when in the mood **Behavioural substitution (CT)**	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			Be prompted to substitute screen time with other neutral or positive behaviours **Reduce negative emotions (SCT)** Be prompted to ask themselves whether eating will change the problem/emotion they currently facing SE 5.6. Express confidence in dealing with lapses **Verbal persuasion about capability (SCT)** Facilitator to mention that lapses are a normal part of the process of change and that they can still make healthier choices as long as they learn how to deal with the lapses **Information about antecedents (SCT)** Identify the lapse example (eating biscuits) among the factors (social and environmental events, emotions, and cognitions) that lead to the lapse and its	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			consequences Put a chain of antecedents (events, emotions, cognitions), lapse (unhealthy eating, social event), and consequences in the right order. **Problem solving (SCT)** Analyse the above factors, lapse, and consequences, and generate strategies to overcome them **Verbal persuasion about capability (SCT)** Facilitator to reaffirm that participants can successfully overcome future lapses by reflecting on previous ones **Reduce negative emotions (SCT)** Distinguish a behavioural lapse from a relapse Receive advice on the use of a 5-step cognitive strategy to reduce negative emotions in order to deal successfully with a lapse.	

Table 7.3 Matrix for change objectives aiming to increase physical activity to the extent of at least meeting the PA guidelines (behaviour)

Performance objectives	**Behavioural determinants** **Outcome expectations (physical, social, self-evaluative)**	**Knowledge**	**Self-efficacy**	**Goals**
PO 1. Reduce sedentary behaviours	OE 1.1. Assess their current PA and evaluate required PA changes **Feedback on behaviour (CT)** Complete a quiz about physical activity levels and receive written feedback based on their score. OE 1.2. Understand the difference between physical activity and exercise **Framing/reframing (CT)** Understand that exercise is only one of a range of physical activities that can promote health	KN 1.1. Recognise the benefits of PA **Information about health and emotional consequences (SCT)** Know about the physical and emotional benefits of physical activity Know about the link between physical activity and sleep	SE 1.1. Express confidence in being more physically active **Problem solving (SCT)** Identify potential barriers to physical activity and generate strategies to overcome them SE 1.2. Express confidence in reducing sedentary behaviours **Instructions on how to perform the behaviour (SCT)** Recognise ways of reducing sedentary behaviours Recognise ways of improving sleep quality	GO 1.1 Set a goal to reduce sedentary time **Behavioural goal setting (SCT)** Set a SMART physical activity goal based on GO 4.1.
PO 2. Increase lifestyle activities	OE 2.1. Express confidence in (not) seeking social support **Problem solving and social support (unspecified) (SCT)**	KN 2.1. Describe the PA recommendations **Instructions on how to perform the behaviour (SCT)** Know the PA recommendations	SE 2.1. Express confidence in increasing lifestyle activities **Instructions on how to perform the behaviour (SCT)**	GO 2.1. Set a physical activity goal **Behavioural goal setting (SCT)** Set a SMART physical activity goal based on GO 4.1.

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	Identify helpful and unhelpful social support towards PA changes (e.g. family, friends, health care professionals) Problem solve potential social impediments OE 2.2 Be aware that others also face difficulties being physically active after cancer treatment and increase motivation to be more active **Information about others' approval (SCT)** Read motivational quotes from other cancer survivors about physical activity OE 2.3. Increase expectation that health care professionals will approve their lifestyle changes **Credible source (SCT)** Read information from nurses in favour of physical activity		Recognise ways of increasing lifestyle activities	

Performance objectives	**Behavioural determinants** **Outcome expectations (physical, social, self-evaluative)**	**Knowledge**	**Self-efficacy**	**Goals**
PO 3. Increase organised activities		KN 3.1. Recognise safety issues while physically active **Instructions on how to perform the behaviour (SCT)** Recognise when and how to start and stop exercising	SE 3.1. Express confidence in doing more strength, balance, and flexibility exercises **Demonstration of the behaviour & instructions on how to perform the behaviour (SCT)** Provide pictures of cancer survivors demonstrating sample strength, balance, and flexibility exercises and instructions of how to perform those **Behavioural practice/rehearsal (SCT)** Practice some of the resistance exercises during the session following the booklet's instructions	GO 3.1. Plan in detail their organised PA **Problem solving and action planning (SCT)** Recognise ways of organised PA Identify what activities they could do Examine where and when they will do the activity Examine where and when they will do the activity Examine if they need to involve others Question if they will keep it up Examine if they need to travel Examine if it is safe to exercise GO 3.2. Set a goal to increase

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
				organised activities **Behavioural goal setting (SCT)** Set a SMART physical activity goal based on GO 4.1.
PO 4. Create and maintain a discrepancy-reducing feedback loop	OE 4.1. Express confidence in their ability to change their behaviour **Pros and cons (SCT)** Explain of the components of motivation to change Review examples of advantages and disadvantages for (not) changing their lifestyle Analyse their advantages and disadvantages of (not) changing their lifestyle OE. 4.2. Recognise the importance of making one behaviour change at a time **Framing / reframing (CT)** Recognise that making one behaviour change at a time will be more advantageous in the long		SE 4.1. Express confidence in their ability to increase their willpower **Verbal and written persuasion about capabilities (SCT)** Understand that willpower is a practicable skill (written) Understand that they can learn to swap unhealthy habits to healthy ones SE 4.2. Express confidence in setting SMART healthy eating goals **Behavioural practice (SCT)** Define the principles of SMART goal setting Practise translating vague goals to SMART ones	GO 4.1. Compose an action plan towards increasing PA **Action planning and goal setting (behaviour) (SCT)** Plan in detail the performance of their first SMART goal Plan things that might get in the way of achieving the goal Plan how and when they will review the goal Plan who might help them GO 4.4. Compare PA to personal goals and guidelines **Self-monitoring on behaviour and goal setting (behaviour) (CT)** Review their SMART goal Evaluate outcome of their

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	term compared to making too many changes at once OE 4.3. Recognise the value of self-monitoring and become aware of their PA pattern **Self-monitoring of behaviour (CT)** Verbal and written explanation that self-monitoring of behaviour can improve behaviour practice and maintenance Be prompted to use a pedometer Provision of activity diaries Record the amount and type of moderate PA each day using (if preferred) the Shape-Up diary Record pedometer count OE 4.5. Express confidence in (not) seeking social support **Problem solving and social support (unspecified) (SCT)**		SE 4.3. Express confidence in rewarding themselves for achieving their SMART goals **Self-incentive & non-specific incentive (SCT)** List their own potential rewards SE 4.4. Decide if discrepancies exist when comparing PA to personal goals and guidelines **Discrepancy between current behaviour and goal (CT)** Compare their pedometer count and moderate PA (SE 5.2) to personal goals or guidelines in order to draw attention to the discrepancy. SE 4.5 Maintain self-monitoring through diaries **Problem solving (SCT)** Identify as a group barriers to keeping a food and activity diary	SMART goal

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	Identify helpful and unhelpful social support towards PA changes (e.g. family, friends, health care professionals) Problem solve potential social impediments OE 4.6. Plan their self-reward **Self-incentive & non-specific incentive (SCT)** Understand the value of rewards for achieving their SMART goals Brainstorm ideas for non-food incentives Plan to reward self when they review their goals if they achieve their SMART goals OE 4.7 Reward success **Social reward (SCT)** Facilitator verbally praises participants if and only if participants have progressed with their goals		Discuss ways in which they can overcome the barriers SE 4.6. Express confidence in achieving SMART goals **Review of behavioural goals, problem solving, and social support (unspecified) (SCT)** Re-examine their behaviours. Facilitator and group members provide evaluative feedback if they have (not) met the SMART criteria and if they have rewarded themselves for achieving the goal. Participants should problem-solve themselves with the help of the rest of the group ways of making their goals fit with the SMART criteria	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	OE 4.8. Receive support from each other while making behavioural changes **Social support (unspecified) (SCT)** Distribute to each other their contact details so that they support each other on the behavioural changes during the program Be aware that others also face difficulties following a healthy lifestyle after cancer treatment Get support and ideas from group members on following a healthy lifestyle OE 4.9. Identify potential sources of external support at the end of the programme **Social support (unspecified) (SCT)** Discuss if continuous support from other healthy lifestyle services can be helpful after the			

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
	end of the programme Advice on how they can find information about support in their local area			
PO 5. Deal effectively with triggers of sedentary behaviours and lapses			SE 5.1. Express confidence in dealing with external triggers **Avoidance/reducing exposure to cues for the behaviour (CT)** Be prompted to identify and try to avoid cues promoting PA (e.g. watching a boxset) **Distraction (CT)** Be prompted to use an alternative focus for attention to avoid triggers for screen time **Problem solving (SCT)** Be prompted to identify the triggers for sedentary behaviours and generate a strategy to	GO 5.1. See GO 4.1

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			overcome them (e.g. have an alternative PA plan in case of foul weather)	
			SE 5.4. Express confidence in dealing with fatigue	
			Problem solving (SCT)	
			Understand what fatigue is	
			Select strategies from a list of suggestions to help them overcome fatigue and facilitate physical activity	
			SE 5.4. Express confidence in dealing with unhelpful thoughts	
			Behavioural practice (SCT)	
			Practice translating unhelpful thoughts that might impede healthy eating goals to helpful ones	
			Self-talk (SCT)	
			When experiencing an unhelpful thought, be prompted to remind themselves what they are trying	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			to achieve and why SE 5.5. Express confidence in dealing with emotions **Distraction (CT)** Identify ways for distracting from the mood Be prompted to focus attention on this alternative way when in the mood **Behavioural substitution (CT)** Be prompted to substitute screen time with other neutral or positive behaviours **Reduce negative emotions (SCT)** Be prompted to ask themselves whether not being active will change the problem/emotion they currently facing SE 5.6. Express confidence in dealing with lapses **Reduce negative emotions**	

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy	Goals
			(SCT)	
			Distinguish a behavioural lapse from a relapse	Distinguish a lapse from a relapse
			Receive advice on the use of a 5-step cognitive strategy to reduce negative emotions in order to deal successfully with a lapse.	
			Information about antecedents (SCT)	
			Put a chain of antecedents (events, emotions, cognitions), lapse (sedentary behaviour), and consequences in the right order.	
			Problem solving (SCT)	
			Analyse the above factors, lapse, and consequences, and generate strategies to overcome them	
			Verbal persuasion about capability (SCT)	
			Facilitator to reaffirm that participants can successfully overcome future lapses by reflecting on previous ones	

7.7.4 Make adaptations (Step 4)

7.7.4.1 Prepare design documents for adaptation (4A)

The production of the materials was based on the planned changes. The iterative review process ensured the optimal match between program goals and materials. The Flesch Reading Ease score was 90.8/100 indicating that the text was very easy to read, the text was written in active voice, and included only messages relevant to the change objectives and text with appropriate context. Checklists encouraged interaction and careful hierarchy aimed to support comprehension. The "Eatwell plate" was used as a visual cue and there was higher contrast between ink and paper compared to the original manual, as suggested by survivors.

7.7.4.2 Pre-test adapted materials (4B)

While originally planned, time constraints prohibited pretesting of the adapted materials. However, participants from the pilot evaluation of the program (DEUS pilot study) were expected to provide rich feedback through open-ended questions about the delivery and the materials of the program upon completion of the intervention. These are detailed in the next chapter.

7.7.4.3 Produce final adaptations (4C)

The electronic copy (227 pages) of the final "Shape-Up following cancer treatment" manual is available in the accompanying CD-ROM (Koutoukidis et al., 2015b). This copy was used for the evaluation of the program (Step 6).

7.7.5 Step 5: plan for implementation (Step 5)

7.7.5.1 Identify implementers, implementation behaviours, and outcomes (5A)

For the original program, health professionals, people with interest in the area, and previous "Shape-Up" participants were trained by Weight Concern and followed a scripted manual for facilitating the delivery of the intervention. The delivery of the program required only one trained person, but delivery by two implementers might also be appropriate in case of unexpected circumstances. From the implementers'[19] perspective, the original implementation protocol was deemed sufficient for adoption in the new setting. This also followed the suggestions from the qualitative work mentioned previously. Therefore, potential implementers were not involved at this stage.

As proximity comprised a significant barrier for participation, the pilot intervention, described in the next chapter, physically took place in one of the recruitment hospitals in central London aiming to provide a location easily accessed by transport. Based on the London areas covered by the two recruitment hospitals, it was anticipated that most participants would need to commute less than 45 minutes to participate in the group sessions.

The current community evaluation of "Shape-Up" is primarily based on attendance rate and weight measurements. While attendance rate might be one of the most important sustainability criterion to assess intervention adherence, weight tracking was deemed inappropriate due to the lack of focus on weight loss. Therefore, other criteria such as assessments of health status and HRQoL might be well placed to determine program sustainability. One such tool might be the ATLanTiC (Adaptive Tests for Long-Term

[19] Implementers are called facilitators in the "Shape-Up" program.

Conditions) computer-based system to assess quality of life (Gibbons, 2015), but the final instruments are yet to be defined following the feasibility evaluation. Additionally, a second implementer can attend one random session of at least 50% of the programs to assess protocol fidelity. The implementation outcomes were expected to be 90% fidelity and at least 65% adherence, as defined by attendance of sessions.

7.7.5.2 Develop implementation scope, sequence, and instructions (5B)

The similarities of the implementers for the two program versions, and, therefore, the similarities in the behavioural determinants led to identical matrices of change objectives for effectively facilitating a group (Table 7.4). However, it was deemed appropriate to modify the facilitator's manual so that it reflects the changes in the new program and the unique challenges that this population experience. The 158-page manual provided detailed directions on setting up the program, addressed common challenges in group settings, and contained explicit instructions for the delivery of the program. The scope of the program was delivery of eight 90-minute sessions once per week for eight weeks in groups of 8-12 participants. The sequence was described by the sequence of the topics in the program as shown in Table 7.5.

Table 7.4 Matrix for change objectives for effectively facilitating a "Shape-Up" or a "Shape-Up following cancer treatment" group (behaviour)

Performance objectives	**Behavioural determinants** **Outcome expectations (physical, social, self-evaluative)**	**Knowledge**	**Self-efficacy**
PO 1. Set up the group	OE 1.1. Understand the purpose of the program **Framing/reframing (CT)** Written and verbal explanation of the scope and aims of the	KN 1.1. Understand what is needed to set up a group **Instructions on how to perform the behaviour (SCT)** Provision with detailed instructions on how to set	SE 1.1. Express confidence in setting up the group **Instructions on how to perform the behaviour (SCT)** Provision with detailed verbal and written instructions on how to set

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy
	programme Written and verbal explanation of the evidence-base behind the program	up a group	up a group Written and verbal suggestions for problem solving common issues
PO 2. Run the group	OE 1.1. Understand the value of following the structured program intact **Framing/reframing (CT)** Written and verbal explanation that the participants will benefit most if the program is being followed intact OE 1.1. Understand the responsibilities, perceived benefits as implementer **Framing/reframing (CT)** Written explanation about their responsibilities as an implementer Written explanation about potential benefits as an implementer OE 1.1. Understand the value of the group format **Framing/reframing (CT)** Written explanation about value of the group setting in promoting behaviour change Written explanation about value of the self-help in a	KN 1.1. Understand the program structure and components **Instructions on how to perform the behaviour (SCT)** Principles of facilitation Define the principles of SMART goal setting, self-monitoring, and self-incentives Provision with a detailed manual with detailed instructions of what to do in each session	SE 1.1. Express confidence on running the program effectively **Instructions on how to perform the behaviour (SCT)** Provision with a detailed manual with detailed instructions of what to do in each session Written recommendations on dealing with issues / problems common to the "Shape-Up" groups Written recommendations on dealing with issues / problems common in any group setting **Social support (unspecified) (SCT)** Discuss in the facilitators' forum arisen issues and problem solve potential solutions Contact program developers for arisen issues and problems **Behavioural practice (SCT)** Define the principles of SMART goal setting, self-monitoring, and self-incentives Practise translating vague goals to SMART ones

Performance objectives	Behavioural determinants Outcome expectations (physical, social, self-evaluative)	Knowledge	Self-efficacy
	group setting		Brainstorm potential self-incentives **Behavioural practice (SCT) and problem solving (SCT)** Practise problem solving common challenges in "Shape-Up" groups during the training session to increase skill

Table 7.5 Structure and content of the Shape-up following cancer treatment sessions

# Session	Session title	Session content	Approximate time
Session 1	Preparing to Shape-Up	Welcome & introduction to the programme	25min
		Setting ground rules for the group	10min
		Discussion about previous experience of diet and physical activity changes, how cancer has shaped their eating and activity patterns, and hopes and fears about the programme	15min
		Motivation for change	10min
		Break	5min
		Setting a lifestyle target	10min
		Information and discussion about the importance of self-monitoring and food diaries	10min
		Round-up, and preparation for next session	5min
		Take home message	5min
Session 2	Keeping to a regular eating pattern	Review: Discussion about self-monitoring and food diaries, and goal progress	20min
		Volunteer-led discussion: Keeping to a regular eating pattern Key learning points: The importance of keeping to a regular eating pattern, the definition of a regular eating pattern, the importance of breakfast, suggestions for goals, disadvantages of eating regularly.	40min
		Break	5min
		New topic: Goals and rewards Discussion about the principles of goal-setting, group exercise about setting SMART goals, exercise about goal planning, discussion about rewards, and group exercise about non-food rewards	15min

# Session	Session title	Session content	Approximate time
		Round-up, and preparation for next session	5min
		Take home message	5min
Session 3	Physical activity	Review: Discussion about keeping a diary, setting a regular eating goal, goal-setting, and rewards, goal progress	20min
		Volunteer-led discussion: Physical activity Key learning points: The importance of physical activity for health and wellbeing, the difference between physical activity and exercise, goals to aim for (30 minute of moderate physical activity per day and muscle fitness exercises twice a week), the importance of incremental increase in physical activity levels.	30min
		Break	10min
		Setting an activity goal: individual exercise to help them focus on what they need to think about in order to improve their activity levels and group exercise for improving goal-setting skills	15min
		Round-up, and preparation for next session	10min
		Take home message	5min
Session 4	Eating a balanced diet	Review: Discussion about last week's topics and creating a physical activity goal, goal progress	20min
		Volunteer-led discussion: Getting a healthier balance of foods. Key learning points: the five food groups, what foods to make choose (Plenty of whole grains, fruits, and vegetables; moderate amounts from the "meat, fish and alternatives" and "milk and dairy" groups, preferably low-fat; have little amounts of "foods high in fat or sugar" and prefer healthy oils; limit processed meat, and sugary and alcoholic drinks; prefer foods low in salt).	30min
		Break	5min
		New topic: Lapses	25min

# Session	Session title	Session content	Approximate time
		Information, group exercise, and discussion on how to deal with lapses	
		Round-up, and preparation for next session	5min
		Take home message	5min
Session 5	Keeping an eye on food serving sizes	Review: Discussion about last week's topics, goal progress, and exercise about managing lapses	20min
		Volunteer-led discussion: Keeping an eye on food serving sizes	50min
		Key learning points: Each participant brings a weighted portion of some foods and group members discuss about the understanding food serving sizes and how many servings they should aim for (The food servings are reflecting a 2,000kcal diet for women).	
		Break	10min
		Round-up, and preparation for next session	5min
		Take home message	5min
Session 6	External triggers	Review: Discussion about last week's topics, and goal progress	20min
		Volunteer-led discussion: External triggers	35min
		Key learning points: The difference between external and internal triggers, and main strategies for dealing with external triggers	
		Break	5min
		New topic: Internal triggers	20min
		Discussion about hunger and cravings, group exercise for the dealing with cravings and the difference between craving and hunger, and discussion about fatigue	
		Round-up, and preparation for next session	5min
		Take home message	5min

# Session	Session title	Session content	Approximate time
Session 7	Internal triggers	Review: Discussion about last week's topics, goal progress, and feelings about the group coming to an end	20min
		Volunteer-led discussion: Internal triggers Key learning points: Definition of internal triggers (hunger, cravings, fatigue, emotions, and unhelpful thoughts) and strategies to deal with those	40min
		Break	5min
		New topic: Lapse chains Information about lapse chains and group exercise of putting together a behaviour chain	10min
		Round-up, and preparation for next session	10min
		Take home message	5min
Session 8	Food labels and the *Shape-Up* Change plan	Review: Discussion about last week's topics, goal progress, and reviewing earlier areas of the programme	10min
		Volunteer-led discussion: Food labels Key learning points: The ingredient list and the various names of sugar and saturated fat in food labels, the importance of checking the sugar, saturated fat, and salt content in the labels, and tips for smart shopping	30min
		Break	5min
		New topic: The *Shape-Up* Change plan Information about how to complete a *Shape-Up* change plan and individual exercise on filling a mock plan	20min
		Discussion: Group members discuss their change plan, they re-evaluate their lifestyle target from Session 1, and are given information about the importance of continuing with self-monitoring	20min

# Session	Session title	Session content	Approximate time
		Round-up, and maintaining changes for the long term	5min
		Take home message	5min

7.7.5.3 Plan activities to motivate and train for implementation (5C)

A one-day training session of the implementers for the original program had been developed. It explained the theory of the program, its core elements, quality of delivery, management of challenging situations, and directions for setting up a group targeted outcome expectations, knowledge, and self-efficacy as detailed on Table 7.4. Given the similarities of delivery, content, and behaviour techniques of the two programs, a short briefing explaining the differences between the two programs would be added in the original training with the aim to merge the training for both programs.

7.7.5.4 Plan logistics including budget, staffing, and materials (5D)

The estimated printing cost for one "Shape-Up following cancer treatment" manual was £14.95 (exclusive of VAT) based on a bulk order of 100 manuals in 2015. The remaining logistics were similar to the original program with the facilitators' training to cost £195 per trainee in 2015, inclusive of the facilitator's manual. Taking into account the facilitator's training, booklet production, and dietitian's salary (£20 per hour, 2 hours per session) and assuming 8 participants per group session and free hiring of a community space, the cost of the intervention was estimated to be £9.92 per participant per session or £79.33 per participant for the whole program. Delivery of the intervention by trained volunteers halves the program cost (£39.33 per participant).

7.7.6 Plan for evaluation (Step 6)

The evaluation of the program is described in the next chapter.

7.8 Discussion

The current chapter presented the adaptation process of an evidence-based program focusing on healthy eating and physical activity for endometrial cancer survivors. The use of the IM systematic framework of its adaptation, implementation, and evaluation increases the potential for intervention effectiveness.

The IM framework has been used widely for the development of health promotion programs, including nutrition and physical activity (Bartholomew et al., 2011). Some of the evaluated lifestyle programs in cancer survivors have used adapted versions of evidence-based programs. For example, the LEAN study used an adaptation of the Diabetes Prevention Program (Harrigan et al., 2016). However, the majority of them inadequately report their theoretical constructs and BCTs (Stacey et al., 2015).

If successful lifestyle interventions are to shape practice, this requires suitable characterisation methodology and their connection to an analysis of the behaviour. To my knowledge, this is the first report of a systematic development of a healthy eating and physical activity program in cancer survivors. Only one program has been reported in the literature mentioning its development through a systematic framework. The "Kanker Nazorg Wijzer (Cancer Aftercare Guide)" intervention was a web-based holistic intervention addressing psychosocial issues and smoking together with healthy eating and physical activity in cancer survivors. It was also developed using the intervention mapping approach and targeted similar behavioural determinants to the current intervention (i.e. self-efficacy, outcome expectations, knowledge) (Willems et al., 2015). The intervention resulted in significant changes only in vegetable intake among the dietary behaviours and in moderate physical activity among physical activity behaviours but the study was not powered on these outcomes (Kanera et al., 2016). Another physical activity program was

developed using the new COM-B (capability, opportunity, motivation, behaviour) model but it aimed at nurses providing advice to survivors rather than to survivors themselves (Webb et al., 2016a).

Another strength of the dietary advice provided was the release of the updated version of "The Eatwell Plate" a year after the intervention development. The renamed "The Eatwell Guide" reflects more closely the recommendations presented in the booklet (PHE, 2016)

Limitations of this study include its retrospective evaluation and, potentially, the use of many BCTs that have not been identified in systematic reviews. However, the lack of evidence might stem from lack of use of the BCTs or poor reporting rather than evidence of absence of their effectiveness. Furthermore, the combination of all those BCTs seems to make the "Shape-Up" effective, rather than each specific BCT given the multiple performance objectives it addresses. Moreover, it is generally recognised that multi-level interventions are needed for health behaviour changes to be efficacious in the long-term. While the current model comprehensively addressed individual behavioural determinants, it did not consider the environment factors influencing behaviour. Therefore, incorporation of the program in a framework of multi-level interventions could comprehensively address health promotion policy efforts. One such framework is the WCRF-developed NOURISHING framework and the intervention fits well under the section "Nutrition advice and counselling in health care settings" (WCRF, 2016b). Additionally, the COM-B model could have been a new alternative systematic framework for analysing this intervention (Michie et al., 2011) but its lack of extensive field-testing rendered its application cautious.

7.8.1 Conclusion

In conclusion, systematic intervention mapping provided a framework to design a cancer survivor-centred lifestyle intervention. The systematic literature reviews (0 and 0), exploratory cross-sectional study (Chapter 5), and qualitative study (Chapter 6) crucially informed the adaptation process. Survivors welcomed the intervention and provided essential feedback for its adaptation. The evaluation of the program through a pilot randomised controlled trial is described in the next chapter.

Chapter 8 Feasibility of the adapted intervention: primary outcomes of the Diet and Exercise in Uterine Cancer Survivors (DEUS) pilot study

8.1 Introduction[20]

The previous chapters described the literature gap in behaviour change interventions for healthy eating and physical activity in endometrial cancer survivors. Furthermore, one such intervention was systematically tailored to the needs and preferences of this population. This chapter describes the protocol and feasibility outcomes of the pilot testing of this intervention.

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[20] The published trial protocol is reproduced with permission in **Error! Reference source not found.** Koutoukidis, D. A., Beeken, R. J., Manchanda, R., Burnell, M., Knobf, M. T. & Lanceley, A. 2016b. Diet and exercise in uterine cancer survivors (DEUS pilot) - piloting a healthy eating and physical activity program: study protocol for a randomized controlled trial. *Trials,* 17**,** 130.

8.2 Aim

The aim of this pilot study was to assess the feasibility of a manualised healthy eating and physical activity programme in endometrial cancer survivors post active treatment. The main research question was: Is it feasible to design a randomised controlled trial that will assess if the Shape-Up programme is more effective than usual care in improving the health-related quality of life of endometrial cancer survivors?

8.3 Study objectives

8.3.1 Primary research objective

The primary research objective was to assess the feasibility of the overall trial procedures.

8.3.2 Secondary research objectives

Secondary research objectives included:

1. To obtain variance estimates for clinical outcome measures to be used in the large-scale RCT. These will inform primary outcome and measure of the larger trial and, subsequently, the sample size calculation.
2. To assess willingness of the clinical staff to recruit participants
3. To assess willingness of eligible participants to be randomised
4. To examine potential adverse effects of the intervention
5. To perform a basic economic analysis with the aim to inform the larger trial
6. To assess reasons for loss to follow up
7. To access the overall acceptability of the intervention

8.4 Study Design

The DEUS pilot trial was an eight-week, two-arm, individually randomised, controlled pilot trial comparing the use of the "Shape-Up following cancer treatment" programme to usual care. According to MRC guidance for complex interventions (Craig et al., 2008), this was a Phase 2 feasibility study. Randomisation was performed with minimisation using a 1:1 allocation. The study protocol followed the TIDieR (Hoffmann et al., 2014) and SPIRIT (Chan et al., 2013) checklists, which are available as additional files to the published protocol (Koutoukidis et al., 2016b). The trial has been registered on a relevant registry (ClinicalTrials.gov identifier: NCT02433080).

8.5 Methods: Participants, interventions, and outcomes

8.5.1 Study setting

The recruitment sites were University College London Hospitals NHS Foundation Trust, and Barts Health NHS Foundation Trust; two major academic hospitals in London. The choice of hospitals was driven by their endometrial cancer statistics from the National Cancer Registration Service. The intervention group sessions took place at the University College Hospital Macmillan Cancer Centre in central London. All assessments (approx. 1.5hours each) were performed at The Institute of Sport Exercise and Health.

8.5.2 Selection of subjects

8.5.2.1 Inclusion criteria

Women aged >18 years (no upper age limit) who had been diagnosed with endometrial cancer (ICD C54.1) within the previous 36 months were eligible to take part in the study. They must have also been able to understand spoken and written English. The cut-off of

36 months was chosen to account for the duration of treatment and allow for a sufficient pool of survivors for recruitment so that the presence of the teachable moment and the elimination of early major treatment effects could be balanced.

8.5.2.2 Exclusion criteria

Women who met at least one of the following criteria were excluded:

1. Women with stage IVB (metastatic) endometrial cancer (any metastasis beyond the pelvis)
2. Women on active anti-cancer, and/or palliative treatment
3. Women with second primary cancer
4. Women who lacked mental capacity to decide to take part in the study and to participate in it (upon clinical team's judgement in accordance with the Mental Capacity Act 2005 Code of Practice 2007)
5. Women with severe depression (upon consultant's judgement based on the DSM-IV criteria)
6. Women unavailable for longitudinal follow-up assessments
7. Women who participated in a professionally delivered weight loss or exercise program during the previous 6 months
8. Women with a WHO performance score 3-4 (Oken et al., 1982)

These criteria complied with all but the disability category in the NICE Equality Impact Assessment for lifestyle weight management services (NICE, 2014b).

8.5.3 Interventions

8.5.3.1 Shape-Up following cancer treatment

On top of usual care, intervention arm participants were assigned to groups of three to eight, although the initial plan was that they would be assigned in groups of eight to ten. The allocation to groups was on a first-come first-served basis to avoid delays in delivering the intervention to randomised participants, which might have increased dropout rates. The five groups met every week for eight weeks and each session lasted approximately 90 minutes. Participants were offered a range of times and dates for the sessions.

Following training by Weight Concern, I facilitated the "Shape-Up following cancer treatment" sessions using the standardised and scripted protocol. An extra trained provider (Sonia Lopes, Jessica Haddrell, Anna Roberts, and Nathalie Kliemann) attended the meetings of the four groups to aid with facilitation but did not participate in the discussion. I ran the last group by myself due to last minute cancellation of the facilitator.

The intervention was under the tier 2 weight management services (DoH, 2013a) and in accordance with NICE guidance on lifestyle weight management services (NICE, 2014b) and individual approaches to behaviour change (NICE, 2014a). The intervention has been detailed in 0 with its structure and content described in Table 7.5.

8.5.3.2 Care as usual

Participants in the control arm were offered usual care. Quantifying usual care was challenging, but the qualitative study in Chapter 6 indicated that lifestyle advice is limited in the current clinical setting. During the trial, participants were only contacted for the assessments. After the final follow-up, I had a five-minute discussion with them using a standard statement focusing on the link between lifestyle and health consequences and

targeting their motivation to improve their health. At that point, they also received the "Healthy living after cancer" booklet; a brief self-help manual produced by the World Cancer Research Fund (WCRF, 2015). By providing only this information, we aimed to match the currently offered usual care as accurately as possible but also meet ethical standards.

8.5.4 Primary outcome measures

The primary outcome measures for the pilot trial were:

1. The recruitment rate
2. The adherence (attendance of the sessions)
3. The retention rate (complete follow-up)

The main criterion to judge the pilot study successful and a large-scale RCT feasible using the recruitment measure was recruiting (consenting) 30% of the eligible participants (32 participants per 110 estimated to be eligible in each centre during the 6 month recruitment). This target seemed reasonable based on previous experience and similar rates indicated in the literature (Daley et al., 2007, Korde et al., 2009).

8.5.5 Recruitment

Potential participants were recruited from the gynaecology outpatient clinics at the two hospitals. A member of the clinical team initially identified potential participants from clinic lists. Individual patients were considered for participation by their consultant. If, during the course of a usual clinic appointment, the clinician believed that the patient was suitable for study participation (i.e. not too ill or distressed) they asked the patient if they would be interested to hear about the study. Bright colour reminders were attached at the cover of

the patient notes before their appointment to enhance consultants' engagement with recruitment. After initial screening from the clinician and if the patient was willing to hear about the study, following verbal consent, they were introduced to the researcher (myself or Moscho Michalopoulou) attending the clinic for final screening and a detailed discussion of the study. All participants had to consent for themselves following standard procedures. Recruitment estimate was on average 1.07 participants per week per hospital during the 30-week recruitment period.

The clinical team at UCLH also identified potential participants that had been treated in the two recruitment sites but followed up at local sites. Following GP's verification that the participants were alive, invitation letters signed by the consultant were sent to these women together with the participant information sheet, an opt-in form, the barriers to participation survey (Mills et al., 2006), and a business reply envelope. I contacted the women interested, discussed the study, answered any questions they had and checked they fulfilled the eligibility criteria.

8.5.6 Assignment of interventions

8.5.6.1 Sequence generation

Following written consent, individuals were randomised with a 1:1 allocation to receive either the active intervention or care as usual through minimisation. This allocation process is recommended in small trials to ensure balance between groups (Altman and Bland, 2005). The two stratified variables were age (cut-off: 61 years) and obesity (BMI cut-off: 30kg/m^2) being strong prognostic factors of all the clinical outcome measures. The age cut-off was chosen as this is the median age of diagnosis for endometrial cancer (DeSantis et al., 2014) and BMI cut-off is the WHO cut-off to classify obesity.

The allocated treatment was determined using MinimPY software run by Rebecca J. Beeken. Initially, the first participant was randomly allocated. For each participant following, allocation was based on the imbalance scores, calculated as a function of current allocations after a hypothetical allocation of the new participant in each study arm. The new participant was allocated to the arm with the least imbalance score (Saghaei and Saghaei, 2011). A 20% random element was included in the algorithm (Altman and Bland, 2005).

8.5.6.2 Allocation concealment mechanism

The allocation concealment scheme involved sequentially numbered opaque sealed envelopes that were kept by the researcher (RJB) who generated the allocation sequence and could not have been physically reached by the rest of the research team. The researcher maintained no contact with the rest of the group about the allocation concealment until enough participants were allocated in both groups, so that a "Shape-Up following cancer treatment" group could be performed.

8.5.6.3 Implementation

After performing the baseline assessment, I fed back to RJB the BMI and the age of the recruited participant on a randomisation form in a sequentially numbered opaque sealed envelope. The latter ran the algorithm and allocated the participant. This process continued until enough participants were allocated in both groups to run a "Shape-Up following cancer treatment" group. For example, week 0 started after 8 participants were allocated to each group. Apart from the researcher who assigned participants to the two groups, all research team members were blinded to group allocation until a group could be run (e.g. the first 16 participants had been randomised). At that point, participants were also notified

about their arm allocation. Thus, randomisation was conducted without any influence of the research team, minimising selection bias.

8.5.6.4 Blinding

Due to the nature of the intervention, blinding was not possible for either participants or the researchers delivering the intervention. The independent trained assessor of the 8-week follow-up (Moscho Michalopoulou, an MSc student) was blinded to treatment allocation. She did not have any data about participants' allocation. Participants were also requested not to disclose their allocation treatment. Given resource constraints, I performed the un-blinded 24-week follow-up assessment.

8.5.7 Data collection and processing

Table 8.1 presents the specific assessments at each time point of the study.

8.5.7.1 Recruitment

A hierarchical framework for patient-trial fit, opportunity for trial inclusion, and acceptance for enrolment was used to describe the recruitment process (Kanarek et al., 2012). In contrast with the original framework, the category "patient interested" preceded that of "trial discussed" to fit the current recruitment process. Participants who were introduced to the study and decided not to enrol completed a 25-item investigator-designed survey about barriers to participation based on a previous meta-analysis (Mills et al., 2006). They were informed that they did not need to disclose this information. Enrolled participants were reimbursed for their travel expenses.

Table 8.1 Study assessments at specific time points

		Study Period					
		Screening	Baseline	Allocation	Post-allocation		
SF	Time point		W -3	W 0	W 1	W 8	W 24
	ENROLMENT						
I	Eligibility screen	X					
I	Informed consent	X					
SC	Allocation			X			
	INTERVENTIONS						
I	Shape-Up				▬▬		
I	Usual care				▬▬		
	ASSESSMENTS						
I	Socio-demographic data		X				
I	EORTC-QLQ-C30		X			X	X
I	EORTC-QLQ-EN34		X			X	X
I	Dietary assessment		X			X	X
I	Physical activity		X			X	X
I	Weight		X			X	X
I	Height		X				
I	Body composition		X			X	X
I	Waist circumference		X			X	X
I	Hand-grip strength		X			X	X
I	Blood pressure		X			X	X
I	Shape Up evaluation					X[2]	X[2]
I	Control group input						X[3]
I	Qualitative interviews					X	X
I	Health care resource use						X
I	EQ5D-3L		X				X
SC	Serious adverse events	As needed throughout the protocol					

[1] Closeout for the control group will be at week 40 after receiving the intervention.

[2] Only the intervention group [3] Only in the control group

I: Interviewer, SC: Study Co-ordinator, SF: Staff member, W: Week

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8.5.7.2 Diet

The "Automated Self-Administered 24-Hour" (ASA24®) tool (Subar et al., 2012) was used for dietary assessment with a single weekday recall at each time point. While this is a self-administered tool, participants reported their intake with the assistance of the researcher. ASA24 has acceptable validity with 80% of the items truly consumed reported (Kirkpatrick et al., 2014). It has also been used in trials with cancer survivors (Rock et al., 2013). Piloting the tool in the cross-sectional study showed high acceptability and feasibility but there were some differences in the reported foods. To enhance accuracy, the researcher noted the brand of the consumed food and queried the specific ingredients in each homemade recipe.

Recorded foods were transferred to the DINO (Diet In Nutrients Out) dietary assessment software (MRC Human Nutrition Research Unit, University of Cambridge) (Fitt et al., 2015) that incorporates a British food database, given the country-specific food nutritional composition (Uusitalo et al., 2011). Where applicable, the brand of the food was used in the coding. For ready meals, this included creating the nutritional profile of the meal based on the ingredients and nutrition label using a specifically designed Nutrient Calculator before data coding. Recoding the data included using the UK standard weights for fruits, vegetables, potatoes, eggs, bacon slices, and crackers given large differences with the US database. The same applied for reported intake of oil, butter, margarine, sugar, jams, syrups, and honey in household measures (e.g. teaspoons). Where recipes were mentioned, each ingredient was coded separately using standardised procedures. An experienced independent data analyst scientist (Nida Ziauddeen) guided the process and checked 10% of entries for accuracy.

The Alternative healthy eating index 2010 (AHEI-2010), which scores participants' diet against the recommended healthy eating patterns was calculated based on the 24-hour

recall data on a scale of 0-110 with 110 indicating optimal diet. The score is based on 11 dietary components (vegetables, fruits, whole grains, sugar sweetened beverages, nuts and beans, red and processed meat, polyunsaturated fatty acids, long-chain omega-3 fatty acids, trans fatty acids, alcohol, salt) each contributing equally to the total score (Chiuve et al., 2012). AHEI-2010 was selected because it comprehensively captures diet, strongly predicts survival, and its components are targeted with the intervention. Similar indices have effectively been used in previous trials (Clutter Snyder et al., 2007). The recall was accompanied by a 42-item updated version of the DINE food frequency questionnaire (Roe et al., 1994) together with questions about fruits, and vegetables.

8.5.7.3 Physical activity

Physical activity was assessed using the Stanford 7-Day Physical Activity Recall (Sallis et al., 1985). During a 15-minute interview, the participant recalls the activities the previous seven days. It has shown acceptable reliability and validity (Bonnefoy et al., 2001) and is responsive to change.

8.5.7.3.1 Changes to physical activity outcomes

During the week before the final follow-up, the self-reported physical activity data were supplemented with objectively measured ones using ActivPal™ [21] accelerometers in a subsample of the cohort. Each participant attached the device to the middle of their right thigh following standardised guidelines and using waterproof adhesive dressing over the device. They wore the devices for seven consecutive days including sleep. Participants returned the monitor at the follow-up assessment. Data were exported into Excel from the ActivPal interface program.

[21] www.paltechnologies.com

8.5.7.4 Anthropometry, body composition, and hand grip strength

Weight (to the nearest 0.1kg) and body composition were measured with a multi-frequency segmental body composition analyser (MC-980, Tanita Corp., Tokyo, Japan). Participants were barefoot and held a pair of electrodes attached to the base of the analyser. Body fat was estimated from the electrical impedance. This is because the small electrical current generated by the analyser can penetrate lean tissue and cells but not fat tissue, depending on the electrical frequency at which the measurements are made. Body composition is automatically calculated from a proprietary prediction equation. Visceral fat and metabolic age are also estimated. To ensure stable subject conditions, participants were instructed to abstain from large meals or drinks two hours before the assessment. They emptied their bladder immediately before the assessment and cleaned their limbs with sanitiser to reduce oily or sweaty limbs that can affect measurement accuracy. Measurements are missing for one participant who refused to remove her socks.

Using standardised protocols, height was measured with a stadiometer to the nearest 0.1cm and handgrip strength using a handgrip dynamometer (T.K.K.5401 grip – D, Takei Scientific Instruments, CO., LTD. Tokyo, Japan). Waist circumference was measured with a measurement tape (SECA 201, Seca, Hamburg Germany) to the nearest 0.1cm at the midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid auxiliary line (WHO, 2008).

8.5.7.5 Blood pressure

Blood pressure was measured using an automated sphygmomanometer (Omron) with the participant seated comfortably for five minutes before measurement and their arm supported at the level of the heart. All measurements were taken twice and averaged for analysis.

8.5.7.6 HRQoL

Participants filled out the widely used, reliable, and validated 54-item EORTC QLQ-C30 (Aaronson et al., 1993) and Endometrial Cancer Module (QLQ-EN24) (Greimel et al., 2011).

8.5.7.7 Health care resource use and QALYs

During the final follow-up assessment, participants responded to a health care resource use 6-item questionnaire (Gordon et al., 2012), asking about their potential appointments with their GP or other health care professional, hospital or other health care services, and medication use since the beginning of the intervention. Quality-of-life adjusted years (QALYs) were assessed with the validated 6-item EQ5D-3L (Rabin and de Charro, 2001).

8.5.7.8 Auditing

All sessions were audiotaped. RJB attended one of the group sessions and one of the assessments for quality control.

8.5.7.9 Shape-Up questionnaire and program satisfaction

To assess core components of the intervention, participants responded to a 10-item questionnaire developed as an evaluation tool of the original Shape-Up program. Each item (e.g.: "I can set effective eating and activity goals and work towards them") was scored on a 5-point scale (strongly disagree to strongly agree).

Intervention-arm participants who were engaged with the program completed and posted in a pre-paid envelope an 18-item program evaluation questionnaire with both closed and open questions based on a previously validated evaluation form (Queensland_Health,

2014). The open-ended questions were analysed using manifest content analysis (Hsieh and Shannon, 2005) in Microsoft Office Excel 2011.

8.5.7.10 Control arm contamination

To assess contamination, the control arm completed in the final follow-up two questions assessing any input about diet and physical activity they received from external sources.

8.5.7.11 Interviews with clinicians

Six consultants and two registrars that were recruiting participants from UCLH were interviewed about their views on study recruitment using a semi-structured protocol by phone or face to face. The interviews lasted on average 10 minutes, were digitally recorded, transcribed verbatim by a professional company, and checked for accuracy. Given the structured interview and short replies, data were analysed with content analysis using NVivo version 10 (QSR International Pty Ltd, 2014) software.

8.5.8 Statistical methods

Primary outcomes are reported in proportions with confidence intervals (CIs). Continuous variables are reported by descriptive statistics (non-missing sample size, mean, standard deviation, median, interquartile range). Categorical variables are summarised using frequencies and percentages.

Sample size was estimated considering all three primary outcomes by using the A'Hern's formula for one-stage phase II trials (A'Hern, 2001). Regarding recruitment, a success rate approximately of 30% or more was considered desirable, for the trial to be feasible. A success rate of 15% or less would be unacceptable. The trial tested the null hypothesis H_0 that recruitment would be ≤15% against the alternative hypothesis H_1 that recruitment

would be ≥30%. With a 5% level of significance and 90% power, 64 participants were needed so that we could estimate whether the percentage of participants with successful recruitment was ≤15% or ≥30%. If we could recruit 15, or more, participants, we could reject the null hypothesis.

In addition to recruitment rate, the study also examined adherence rate and retention rate (complete follow-up). Adherence is defined as the proportion of engaged participants attending at least one of the last three sessions of the intervention. Engaged participants were those who attended at least two sessions of the intervention. Best practice guidance suggests that programmes should be commissioned if at least 60% of participants are likely to adhere (DoH, 2013a). A success rate approximately of 85% or more would be desirable. That means that 85% or more of the engaged participants in the intervention group would need to attend at least one of the last three sessions of the intervention. A success rate of 60% or less would be unacceptable. The trial tested the null hypothesis H_0 that adherence would be ≤60% against the alternative hypothesis H_1 that adherence would be ≥85%. With a 5% level of significance and 90% power, 27 participants were needed so that we could estimate whether the percentage of participants with successful adherence is ≤60% or ≥85%. If 21 or more participants successfully adhered, we could reject the null hypothesis.

Regarding complete follow-up, a success rate approximately of 75% or more would be desirable for the trial to be considered feasible. A success rate of 60% or less would be unacceptable. The trial tested the null hypothesis H_0 that complete follow-up would be ≤60% against the alternative hypothesis H_1 that complete follow-up would be ≥75%. With a 5% level of significance and 80% power, 62 participants were needed so that we could estimate whether the percentage of participants with complete follow-up was ≤60% or ≥75%. If 44, or more, participants had a complete follow-up, we could reject the null hypothesis.

Therefore, a sample size of 64 (32 per arm) was deemed sufficient to test the above hypotheses and allow decisions to proceed to a Phase III trial. This sample size also allowed for rich feedback from the participants to be used for the optimisation of the procedures and the materials in the large study. Lastly, it allowed a certain degree of precision in calculating standard deviations for the secondary outcomes that will be the key design parameters for the main study (Teare et al., 2014).

Following verification of assumptions (linearity, homogeneity of regression slopes, approximate normality of the residuals, homoscedasticity, and homogeneity of variances), analysis of covariance (ANCOVA) was used to compare the intervention arm against the control arm in an exploratory way, as the study was not powered to detect differences. The analysis followed the intention-to-treat strategy. Only the eligible participants (n=54) were included in the primary complete case analysis following recommendation of the Trial Steering Committee. A sensitivity intention-to-treat analysis of eligible participants was carried out with multiple imputation of the missing data (Moher et al., 2010); available in **Error! Reference source not found.**.

Adjustment for BMI, age, and baseline value of the outcome (regardless of P-values) was performed with linear regression. Interactions of the adjusted variables with group allocation were tested and found to be primarily non-significantly. As the estimates in the models that included interactions were almost identical to those without interaction terms, only the latter are presented. Details of the statistical analysis are available in **Error! Reference source not found.**. The majority of missing data were missing due to non-attendance at follow-up. The level of statistical significance was set at 5% for the primary outcome measures. Group means are presented with standard deviations (SDs) and between-group mean differences with 95% CIs. Adverse events are reported descriptively. The Statistical Package for Social Sciences (SPSS, Chicago, IL) version 23 was used for the

whole data analysis. Details of the statistical analysis are presented in **Error! Reference source not found.**.

8.6 Results

8.6.1 Recruitment

Recruitment took place over a period of 27 and 18 weeks (April 2015 – December 2015) at UCLH and Barts Health, respectively, as demonstrated in Figure 8.1. Among the first 64 eligible participants approached, 20 consented to participate, leading to rejection of the null hypothesis that recruitment would be ≤15%. Therefore, recruitment continued for enrolling the projected sample of 64 participants.

Table 8.2 shows the number of screened participants at each stage of the recruitment process in the three recruitment settings. The respective proportions are detailed in Table 8.3 and were similar between the two recruitment sites. Out of the 296 eligible participants, 23.6% (95% CI: 18.8, 28.5) consented to take part and 20.3% (95% CI: 15.7, 24.9) enrolled in the study. Therefore, the actual sample (n=60) size reflected 93.8% of the projected one (n=64).

The difference in recruitment period between sites was primarily explained by substantial delay of NHS Research and Development (R&D) management approval at Barts Health. This rendered the planned 30-week recruitment at Barts Health unfeasible considering the study timeline, despite the one-month extension to the recruitment period. Based on the observed recruitment rate at Barts Health, the target sample size could have been reached with an additional five-week recruitment period.

Reasons for non-participation were documented for 36.7% (n=83) of those who were eligible but did not consent and 90.2% of those that were approached. Inconvenience to

everyday life (78%) and transport to trial site (63%) were the main barriers to participation, with further barriers detailed in Figure 8.2. The CONSORT flow diagram shows the progress through the different trial stages (Figure 8.3).

8.6.2 Exclusions

Of the 60 participants recruited, following further post-randomisation eligibility checks six were found to be ineligible. Three were randomised to each arm. Reasons for ineligibility included stage IVB endometrial cancer (n=2), second primary cancer (breast cancer n=2, ovarian cancer n=1), and diagnosis of endometrial hyperplasia instead of endometrial cancer (n=1). Miscommunication between clinicians and researchers, and oversight of the second primary cancer eligibility criterion by the researchers in the first weeks of recruitment accounted for this.

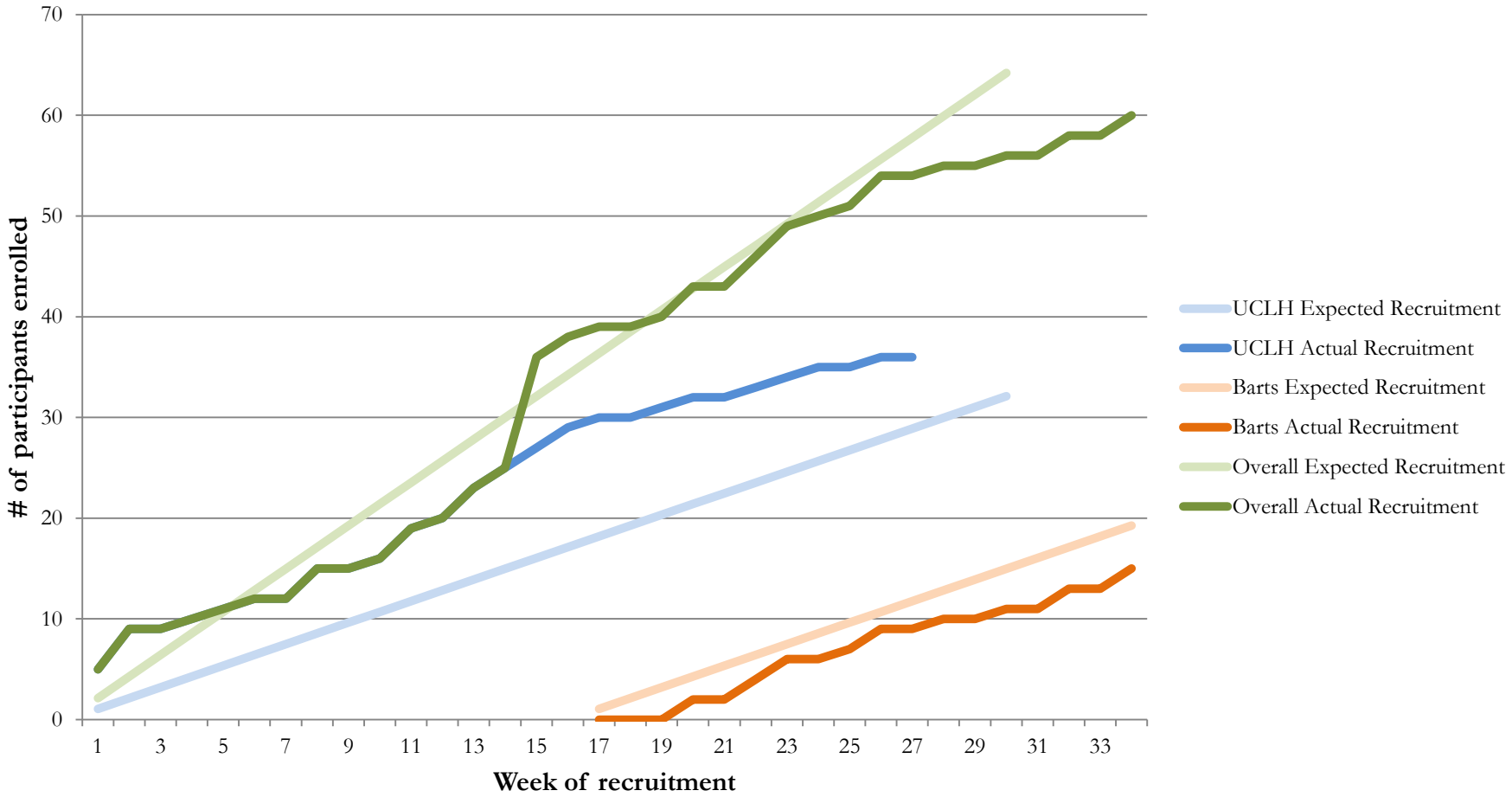

Figure 8.1 Projected and actual recruitment by site

The sharp spike in week 13 in overall recruitment indicated the recruited participants through mail out.

Table 8.2 Number of screened participants at each stage of the recruitment process

	UCLH	Barts	Hospitals combined	Mai-out	Total
1. Women in gynaecologic oncology clinic	**2305**	**1047**	**3352**	**294**	**3646**
Other cancer site - not endometrial cancer	1638	828	2466	36	2502
Stage IVB (metastatic) endometrial cancer	11	7	18	14	32
Active anti-cancer, and/or palliative treatment	164	47	211	3	214
Endometrial Diagnosed >3years	67	49	116	69	185
Second primary cancer	34	8	42	2	44
Duplicates	168	3	171	106	277
2. Available for trial by disease characteristics	**223**	**88**	**311**	**64**	**375**
Not able to understand spoken and written English	23	13	36	1	37
Lack of mental capacity	3	2	5	-	5
Severe depression	2	-	2	-	2
WHO performance score 3-4	7	3	10	5	15
Unavailable for longitudinal follow-up assessments	4	3	7	2	9
Participated in a professionally delivered weight loss or exercise program during the previous 6 months	8	2	10	1	11
3. Eligible for participation	**176**	**65**	**241**	**55**	**296**
Did not attend clinic	23	13	36	-	36
Too distressed	5	-	5	-	5
Clinician did not introduce her to the study because of the long wait	1	-	1	-	1
Clinician did not introduce her due to confusion about eligibility criteria	-	2	2	-	2
Clinician did not introduce her because she had vision difficulties	1	-	1	-	1
Clinician did not introduce her because she was due for a knee operation	1	-	1	-	1
Discussed with clinician and decide not to take part due to travel	2	-	2	-	2
Not approached by clinical team - medical notes missing / no pink leaflet	1	-	1	-	1

	UCLH	Barts	Hospitals combined	Mai-out	Total
Lost her in clinic - clinician forgot to mention study	1	-	1	-	1
Not introduced to the study because researcher not in clinic	1	1	2	-	2
Pregnant	-	1	1	-	1
4. Physician Triage & introduced to the study	**140**	**48**	**188**	**55**	**243**
Not interested to hear about study	23	9	32	-	32
Long wait / too busy to talk about study	2	-	2	-	2
5. Participants interested	**115**	**39**	**154**	**18**	**172**
Lost in clinic - talking to other eligible participants	1	0	1		
6. Trial discussed	**114**	**39**	**153**	**9**	**162**
Decided not to take part and completed barriers survey	49	13	62	9	71
Decided not to take part, gave reasons, but did not complete barriers survey	6	6	12	-	12
Decided not to take part without giving reasons	1	2	3	-	3
Could not be reached back	11	3	14	-	14
Excluded due to cancer recurrence	1	0	1	-	1
7. Participant consented	**46**	**15**	**61**	**9**	**70**
Dropped out due to family reasons	2	-	2	-	2
Dropped out due to feel of no benefit	1	-	1	-	1
Dropped out due to inconvenience to everyday life	3	1	4	-	4
Dropped out due to health reasons	1	1	2	-	2
Not eligible - second primary cancer	1	-	1	-	1
8. Participant enrolled (randomised)	**38**	**13**	**51**	**9**	**60**

Table 8.3 Proportions (95% CIs) of consented & enrolled participants by recruitment site

	UCLH	Barts Health	Both hospitals	Mail-out	Total
Consented participants					
% Of eligible	26.1 (19.6, 32.6)	23.1 (12.8, 33.3)	25.3 (19.8 30.8)	16.4 (6.6, 26.1)	23.6 (18.8, 28.5)
% Of physician triage	32.9 (25.9, 39.8)	31.3 (20.0, 42.5)	32.4 (26.5, 38.4)	-	-
% Of interested	40.0 (32.8, 47.2)	38.5 (26.6, 50.3)	39.6 (33.4, 45.8)	-	-
Enrolled participants					
% Of eligible	21.6 (15.5, 27.7)	20.0 (10.3, 29.7)	21.2 (16.0, 26.3)	16.4 (6.6, 26.1)	20.3 (15.7, 24.9)
% Of physician triage	27.1 (20.6, 33.7)	27.1 (16.3, 37.9)	27.1 (21.5, 32.7)	-	-
% Of interested	33.0 (26.1, 40.0)	33.3 (21.9, 44.8)	33.1 (27.2, 39.1)	-	-
% Of consented	82.6 (77.0, 88.2)	86.7 (78.4, 94.9)	83.6 (78.9, 88.3)	100	85.7 (81.7, 89.7)

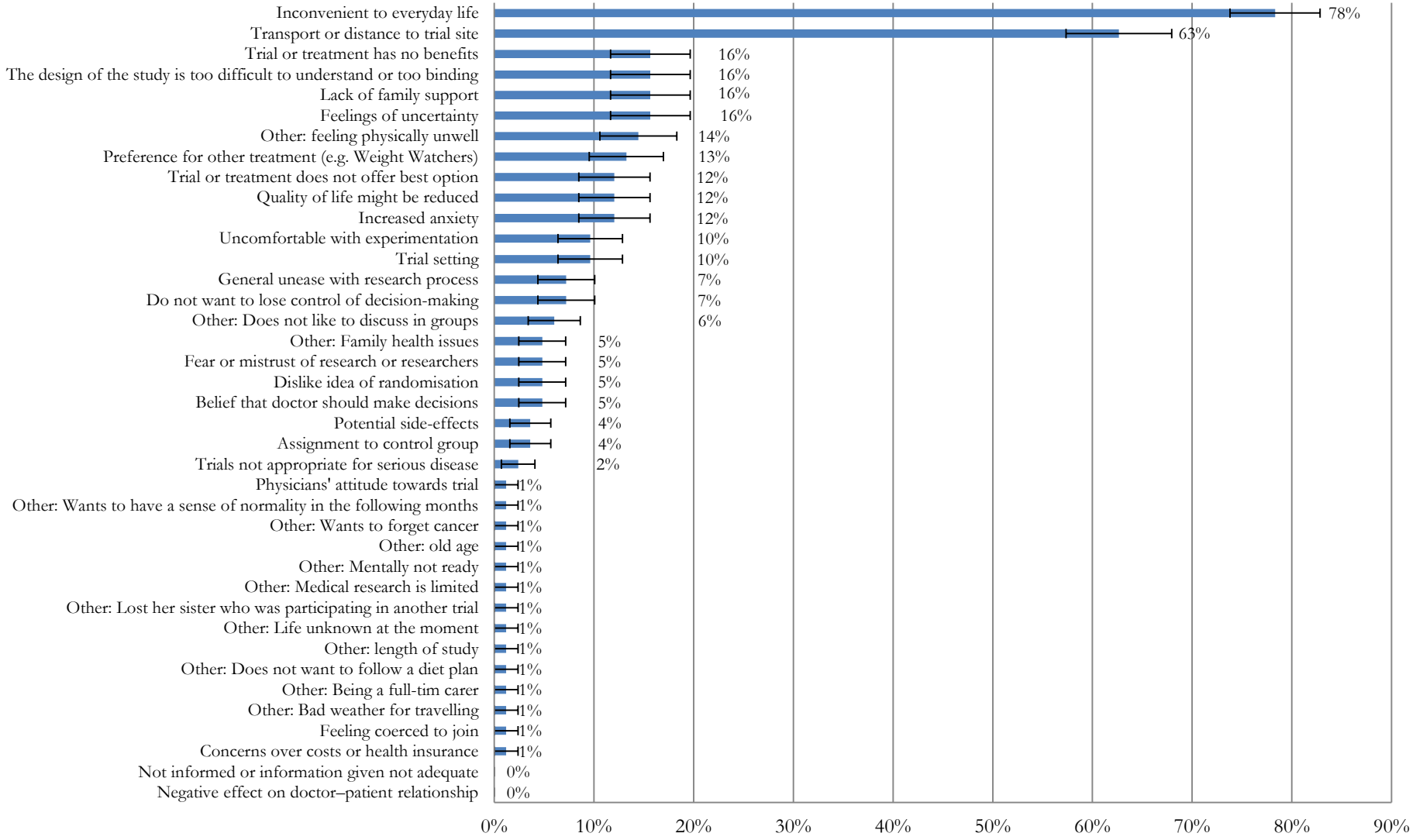

Figure 8.2 Percentage of each barrier to participation with SE (n= 83)

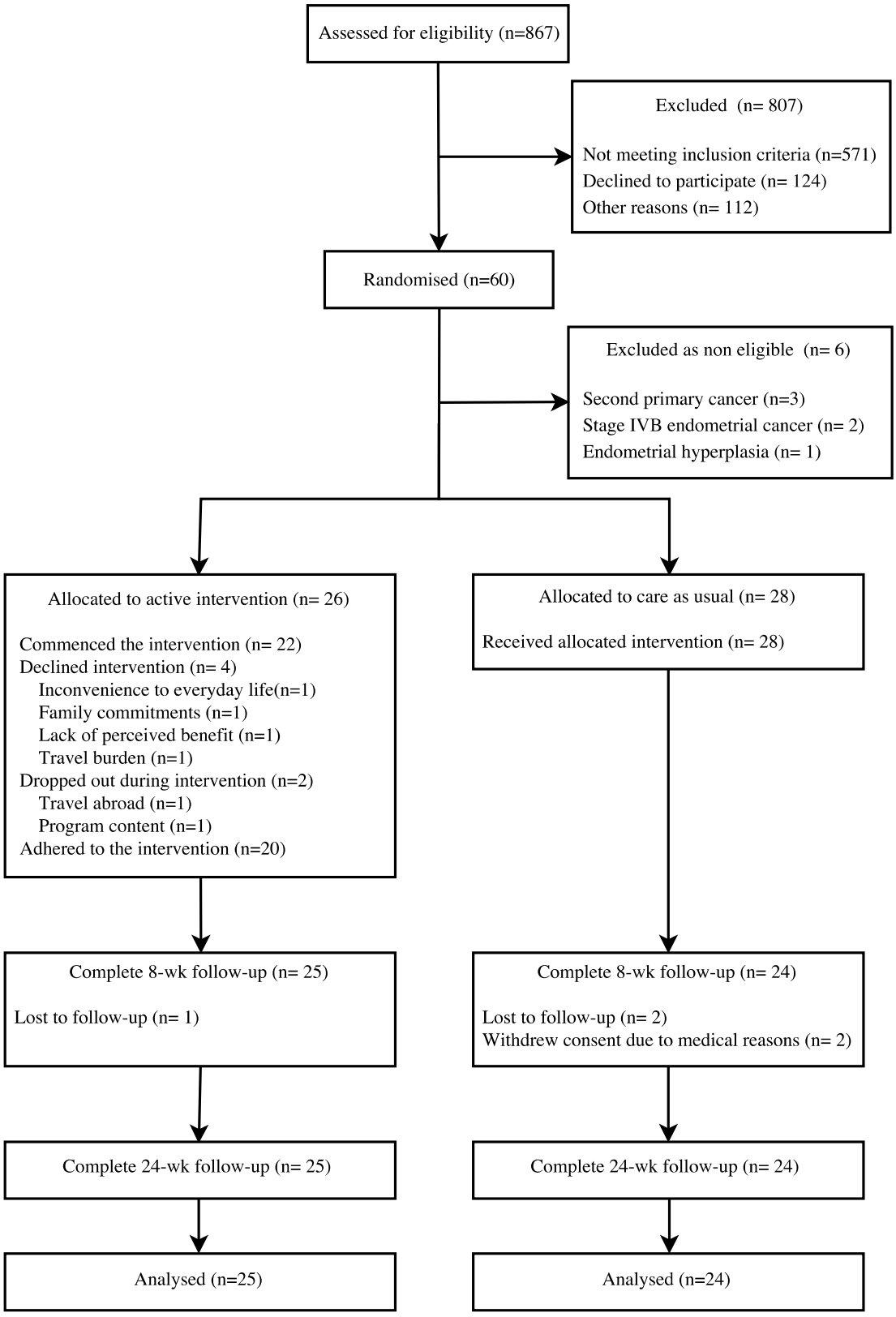

Figure 8.3 CONSORT diagram of the trial

8.6.3 Interviews with clinicians about recruitment

Recruitment did not appear to be consultant dependent, primarily given the rigour of the recruitment process in clinic. Clinicians shared their views about the recruitment process, identifying clinician-centred and patient-centred barriers, as well as potential ways of enhancing recruitment.

8.6.3.1 Clinician-centred barriers to recruitment

Clinicians were supportive of the study and did not have particular concerns about introducing the study to patients. They felt the study might be beneficial to patients.

> *I feel positively towards the study. I'm glad that it's going ahead. I think it's an under-researched area in cancer in a group that have less attention given to them, or just by the nature that they've completed their treatment (*Registrar 1*).*

> *I think education about healthy eating and physical activity is good because a lot of them are obese, a lot of them have been through years and years of dieting and trying to lose weight. So they are a difficult group in that respect, but I think a lot of them are keen, in principle, but need some guidance (Consultant 3).*

However, they were unsure about demonstrable outcome measures given the feasibility nature of the study.

> *Well, I'm not sure whether there are any effects that we can see immediately. It's important that you get a sufficient number recruited to see the feasibility and then plan and design your next step (Consultant 2).*

Clinicians did not perceive that introducing the intervention would affect their relationship with their patients or that the intervention would cause any harm to them.

It [the study] has nothing to do with me and therefore it doesn't affect the relationship (Registrar 1).

I can't see any harm (Consultant 1).

They deemed the current recruitment strategy highly effective, because the burden to their workload was minimised. They mentioned that this was achieved by potentially eligible patients being flagged, researchers being present and reminding them about approaching patients, and through the existence of a separate space for research in clinic.

I think we are doing everything we can by targeting everybody who comes to clinic who is eligible, and putting those pink sheets on is really helpful because otherwise it's really hard to remember to talk to them about it. I usually leave it till the end of the consultation when we are wrapping up the consultation. I say, "Well, you are doing very well, everything looks to be going well," and then I introduce the study, and then as we are leaving you pick them up (Consultant 3).

I think you've got a room to recruit in, you are reminding us, which is important, because I'm terrible. The last thing I'm doing I always forget (Consultant 1).

Not having that preparation makes it [the recruitment] much more difficult. I don't think I would remember to tell all the… you know, given that there are many, many trials that we are recruiting to, it would not be so easily done (Consultant 5).

8.6.3.2 Patient-centred barriers to recruitment

They stressed travelling and commitment to be the main barriers for recruitment.

Transport I think is a big issue. So if you could offer to see them more close to their home, I think that would be probably increase the likelihood that the patient is willing to participate (Consultant 2).

The framing and content of such an intervention was also highlighted as a potential barrier to recruitment. In particular, approaching patients in a non-discriminatory way was deemed to enhance recruitment. Furthermore, framing of its content as a specific lifestyle program was thought to be superior to a weight loss program, strict diet regime, or educational program.

> *If it's framed to them in a way that is non-discriminatory and say, 'We are doing a trial in all patients who have received treatment for endometrial cancer who we know the cancer hasn't come back and that you are quite fit, and we are wondering if you'd be willing to participate in this trial because we know that… well we hope that it will be of benefit to you,' that sort of thing, then it doesn't make people feel like they've got a poor self body image or it doesn't make them feel like they are being discriminated against in any way (*Registrar 1*).*
>
> *So, it's about kind of lifestyle, isn't it? So I think talking about lifestyle. And I think you used that words "can be better". You don't want people to think they are being put on a diet and forced to lose weight (*Registrar 2*).*
>
> *I think it's quite hard in a way to explain to patients that they are not going to be given a specific programme of healthy eating and physical activity. That's the thing that I think patients, to my mind, find the most difficult when I say to them, 'Would you like to take part in this study?' because a lot of them say, 'Ooh yes, I'd like to have a special diet to follow or physical activity,' but when I explain to them that we are not actually giving them a specific programme to follow, it's sort of an educational thing, they are less inclined I think to be particularly keen about the study. […] I think a lot of them assume that this would be a nutritional study, you know, a study of specific nutritional intervention or like a group activity session where they*

actually… like a Weight Watchers programme or something like that. So I think maybe this is quite nebulous to them, just coming to talk about it and educate themselves about it. A lot of them have had a lot of experience of knowing what they should eat, they should do, they just don't actually do it and they need a bit of motivation to do it (Consultant 3).

8.6.3.3 Enhancing recruitment

A potential way for enhancing recruitment was to provide the patients with information about the study in advance of their clinical appointment or while they were waiting for their consultation in clinic.

They get quite psyched up for their three-month follow-up, so a bit anxious. When they are relieved at the end of a consultation that everything is okay and then we start talking to them about the study, that may not be the best time to optimise our uptake, whereas if we've sent them information warning them about it, saying, 'You are well, if you remain well and your doctor is happy that nothing has changed at this appointment, we'd like to invite you to take part in this study' (Consultant 3).

I'm just thinking the time they spend waiting, if there was a way we could make it more useful. […] would it be appropriate for perhaps the CNSs to approach them and have a chat to them and say, 'Look, while you are waiting, the doctor will see you but there might be a half an hour wait, would you mind talking to [a researcher]'? (Consultant 4).

8.6.4 Sample characteristics

Participant characteristics at baseline are shown in Table 8.4. Women were on average (±SD) 62.1 ± 8.3 years old, White (67%), married (53%), 1.2 ± 1.0 years from diagnosis,

with a BMI of 28.0 ± 6.3kg/m^2. They were diagnosed mostly with stage IA (49%), type 1 (82%) endometrial cancer. The characteristics of the whole sample (n=60) are available in

Table 8.4 DEUS pilot study baseline participant characteristics

Characteristic	Shape-Up (n=25)	Care as usual (n=24)	Total
Age, mean (SD)	62.6 (9.0)	61.5 (7.7)	62.1 (8.3)
Race			
White	17 (68)	16 (67)	33 (67)
Asian	4 (16)	5 (21)	9 (18)
Black	3 (12)	1 (4)	4 (8)
Mixed / Other	1 (4)	2 (8)	3 (6)
Living arrangement			
Own outright	12 (48)	10 (42)	22 (45)
Own mortgage	5 (20)	5 (21)	10 (20)
Rent from local authority	6 (24)	5 (21)	11 (22)
Rent privately	2 (8)	4 (17)	6 (12)
Marital status			
Married / living with partner	12 (48)	14 (58)	26 (53)
Married / separated	4 (16)	1 (4)	5 (10)
Divorced	3 (12)	2 (8)	5 (10)
Widowed	2 (8)	4 (17)	6 (12)
Civil partnership	0 (0)	1 (4)	1 (2)
Single	4 (16)	2 (8)	6 (12)
Education			
Degree or higher degree	9 (36)	9 (38)	18 (37)
Higher education below degree level	2 (8)	3 (13)	5 (10)
Secondary education	11 (44)	10 (42)	21 (42)
No formal qualifications	3 (12)	2 (8)	5 (10)
Employment			
Full time / self-employed	9 (36)	11 (46)	20 (41)
Part time	3 (12)	1 (4)	4 (8)
Retired	10 (40)	11 (46)	21 (43)
Other	3 (12)	1 (4)	4 (8)

Characteristic	Shape-Up (n=25)	Care as usual (n=24)	Total
Smoking			
Current	2 (8)	2 (8)	4 (8)
Former	4 (16)	5 (21)	9 (18)
Weekly gross household income estimate (£), median (IQR)	800 (250)	795 (168)	800 (185)
IMD (quintile)			
1 – most deprived	5 (20)	4 (17)	9 (18)
2	9 (36)	6 (25)	15 (31)
3	4 (16)	7 (29)	11 (22)
4	3 (12)	3 (13)	6 (12)
5 – least deprived	4 (16)	4 (17)	8 (16)
Time since diagnosis in years, mean (SD)	1.1 (1.0)	1.4 (1.0)	1.2 (1.0)
Time since diagnosis in months, mean (SD)	19.2 (11.2)	21.4 (11.3)	20.3 (11.2)
Time since completion of primary treatment in years, mean (SD)	0.9 (0.9)	1.2 (1.0)	1.0 (0.9)
Time since completion of primary treatment in months, mean (SD)	17.1 (11.2)	18.5 (11.7)	17.8 (11.3)
Surgery	25 (100)	24 (100)	49 (100)
Chemotherapy treatment	3 (12)	5 (21)	8 (16)
External beam radiotherapy	6 (24)	12 (50)	18 (37)
Brachytherapy	11 (44)	13 (54)	24 (49)
Cancer stage			
IA	11 (44)	13 (54)	24 (49)
IB	11 (44)	6 (25)	17 (35)
II	2 (8)	3 (13)	5 (10)
IIIA	1 (4)	2 (8)	3 (6)
Cancer grade			
1	6 (24)	7 (29)	13 (27)
2	13 (52)	9 (38)	22 (45)
3	6 (24)	8 (33)	14 (29)
Histology			

Characteristic	Shape-Up (n=25)	Care as usual (n=24)	Total
Endometrioid adenocarcinoma	21 (84)	19 (79)	40 (82)
Serous carcinoma	1 (4)	3 (13)	4 (8)
Mixed carcinoma	1 (4)	0 (0)	1 (2)
Serous surface papillary carcinoma	0 (0)	1 (4)	1 (2)
Carcinosarcoma	2 (8)	0 (0)	2 (4)
Adenosquamous carcinoma	0 (0)	1 (4)	1 (2)
Histological type			
Type I	21 (84)	19 (79)	40 (82)
Type II	4 (16)	5 (21)	9 (18)
Charlson Comorbidity Index			
2	18 (75)	21 (84)	39 (80)
3	6 (25)	4 (16)	10 (20)
WHO performance status			
0	20 (83)	20 (80)	40 (82)
1	3 (13)	5 (20)	8 (16)
2	1 (4)	0 (0)	1 (2)
Selected comorbidities			
Diabetes	3 (12)	4 (17)	7 (14)
Hypertension	6 (24)	7 (29)	13 (27)
Dyslipidaemia	3 (12)	3 (13)	6 (12)
Asthma	1 (4)	2 (8)	3 (6)
Osteoporosis	2 (8)	4 (17)	6 (12)
Weight, mean (SD)	69.8 (14.8)	71.9 (15.2)	70.9 (14.9)
BMI, mean (SD)	27.3 (6.5)	28.8 (6.1)	28.0 (6.3)
BMI, median (IQR)	26.2 (24.3)	26.9 (8.6)	26.8 (6l.4)
% Fat, mean (SD)	35.3 (7.7)	36.9 (6.3)	36.1 (7.0)
Metabolic age, mean (SD)	58.9 (14.3)	59.1 (12.7)	59.0 (13.4))
Visceral fat rating, mean (SD)	8.9 (3.3)	9.4 (3.3)	9.1 (3.3)

Percentages might not add to 100 due to rounding
IMD: Index of multiple deprivation, IQR: Interquartile range
Data are presented as n (%) unless otherwise specified
Body composition data for usual care n=23

8.6.5 Adherence

Out of 26 participants in the intervention arm, 21 (81%) engaged and 20 (77%) adhered to the intervention (Table 8.5). Based on the original target of 27 randomised participants in the intervention arm, the study was slightly underpowered to reject the null hypothesis (adherence <60%) but pointed towards this direction.

Median adherence among all randomised participants was somewhat higher in groups 2-4 but similar among groups 1-4 for the engaged and adhered participants (Figure 8.4). Sixty-two per cent of the participants attended at least six sessions (Figure 8.5). The mean overall attendance of sessions was 63% (95% CI: 49%, 77%). The mean attendance of those engaged was 79% (95% CI: 70%, 88%). The mean attendance of those adhered was 82% (95% CI: 74%, 89%). The participants in the fourth and final round of randomisation were split into two small intervention groups for convenience purposes. A participant from the control group that had completed the study was invited to participate in the last group intervention (final n=4 in group 5) to enhance the group experience but was not included in the analysis.

Of the six participants that did not adhere (23.1%), four dropped out before the first session. Reasons included inconvenience to everyday life, travel burden, lack of perceived benefit or family commitments. One dropped out after the first session mentioning that she "did not want to talk about weight and fat" and the other one dropped out after the second session because of long travelling abroad for family reasons. No dropouts occurred in sessions 3-8 (Figure 8.6). Of the 32 absences among the adhered participants, eight were work-related, seven were family-related, six were due to seasonal illness, four due to fatigue, three due to holidays, one due to travel disruption, and one due to other

commitments. No systematic differences in care of participants other than the active intervention (performance bias) were documented. The

Table 8.5 Number of participants randomised, engaged, and adhered by group

	N total	N engaged	N adhered
Group 1 (Saturday morning)	6	4	4
Group 2 (Saturday morning)	6	5	4
Group 3 (weekday early evening)	7	6	6
Group 4 (Saturday morning)	4	4	4
Group 5 (weekday early evening)	3	2	2
Total	26	21	20

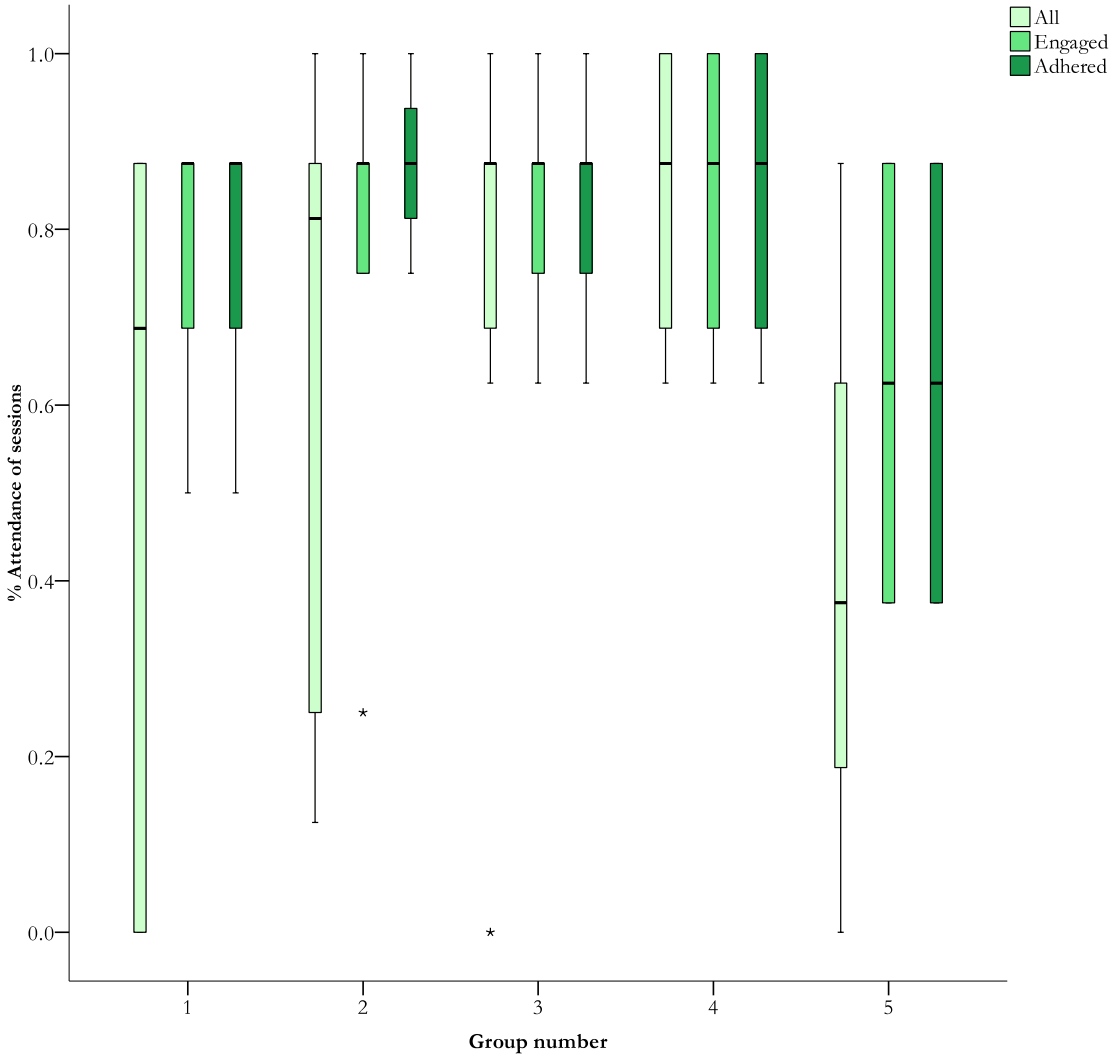

Figure 8.4 Median (IQR) percentage attendance of sessions by group

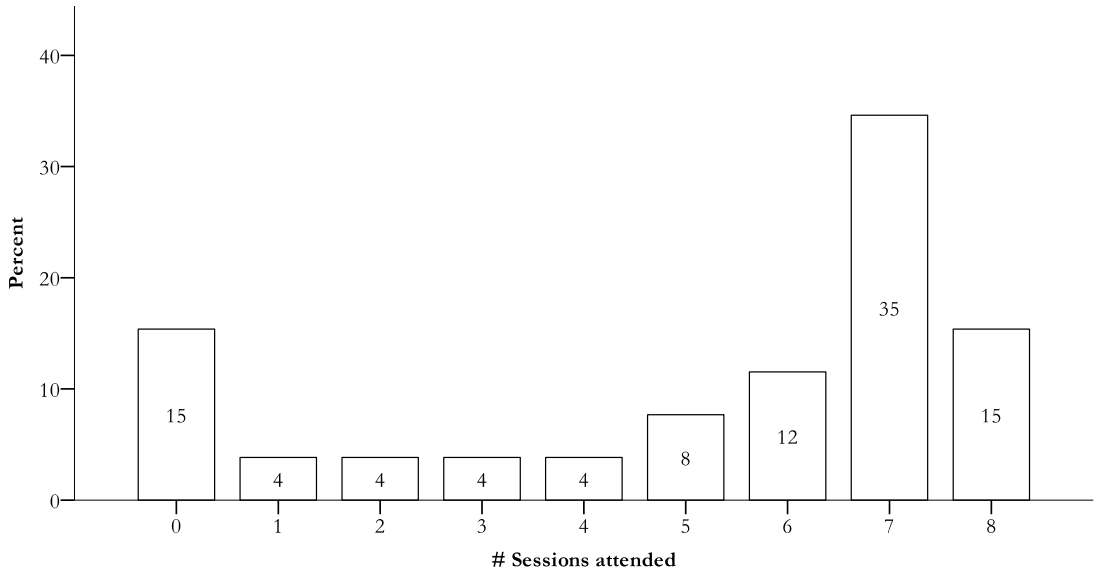

Figure 8.5 Percentage attendance of total number of group sessions

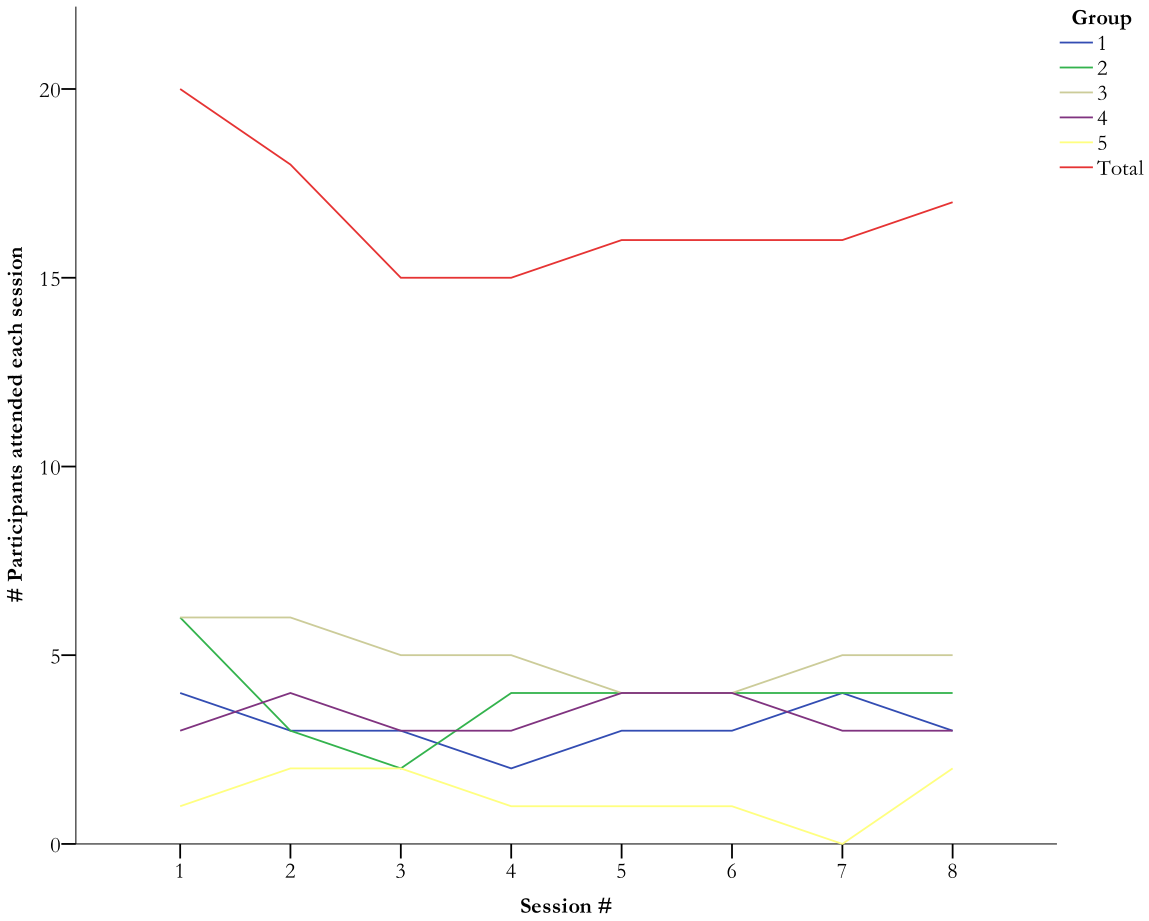

Figure 8.6 Number of participants (total and by group) attended each of the 8 sessions

8.6.6 Program satisfaction

Eighteen participants randomised to the intervention group who adhered provided feedback for the program. They scored the program highly with 44% and 39% reporting that it met or exceeded their expectations, respectively. Two participants (11%) reported that the program sort of met their expectations while 5% mentioned that they didn't know what to expect from the program. The majority (88%) responded that some of the training was review, while only 11% mentioned that all the training was new. About 19% mentioned that some of the training was not relevant. All aspects of the program such as organisation, length, booklet, facilitation were scored highly (Figure 8.8). Additionally, most participants ranked self-monitoring, setting SMART goals, and social support as either very or somewhat helpful in making dietary and physical activity changes (Figure 8.9). In contrast, the responses for self-incentives were mixed with 28% of participants rating it as unhelpful.

Based on the open-ended questions about program evaluation, a range of topics were regarded as most useful (Figure 8.10). Among them, most participants agreed that the sections about keeping an eye on portion sizes, food labelling, and on internal triggers were the most useful. The high program satisfaction was further seconded by the fact that most participants did not regard any topic as least useful. In contrast, others mentioned self-incentives, internal and external triggers, and getting a healthier balance of foods to be the least useful (Figure 8.11). For example, one participant mentioned:

> *I also did not understand the concept of the rewards - better health should be its own reward (Participant in group 4).*

Suggestions for additions to the program were primarily focused on physical activity, such as provision of relevant DVDs, physical activity during the program sessions, and diaries to report physical activity and sedentary behaviour in more detail (Figure 8.12). Most participants did not consider that topics should be eliminated from the program with individual suggestions referring to removal of diaries and quotes of cancer survivors, among others (Figure 8.13).

The opinions about the value of the book content markedly reflected those of the overall program. The section on healthy eating plan, keeping going, food labelling, and the diaries were ranked as the most useful (Figure 8.14), while most participants did not regard any section as least useful (Figure 8.15). Most participants did not suggest changes in the booklet. Others referred to design changes, such as having smaller booklets, reducing wordiness, and removing the word "cancer" from the title. Some favoured more real-life comments, while another participant mentioned that quotes from people "diagnosed with x cancer" were "too hard" (Figure 8.16 and Figure 8.17).

On the one hand, the five most commonly reported factors for getting involved in the program included the peer support of the group, both the focus of the program and their own interest on health promotion, the feeling of giving back for the care they received, the facilitators, and the referral to the program by their doctor (Figure 8.18). On the other hand, most did not report factors discouraging them to participate but others reported these to be the length of the program and the discrepancy between the session dates and their own schedule. Self-monitoring and identification as a cancer survivor were also mentioned (Figure 8.19).

In the additional comment section, participants generally regarded the participation in the programme as a positive experience (Figure 8.20).

Glad I was in the group and not in the control group (Participant in group 2).

It was great - I learnt a lot that I can put into practice. I now have a little voice in my head reminding me to always try or take healthy options! (Participant in group 3)

Suggestions included the addition of follow-up support, and design changes in the booklet, including provision of blank diary copies. A preference for a larger group was mentioned from participants in the smaller groups, as they felt that the peer-education did not work optimally. Regarding the trial procedures, two participants mentioned their difficulty recalling their diet and physical activity and estimating their portion sizes and suggested the provision of plastic utensils during the assessments. Excellent fidelity of the protocol both in the group sessions and the assessments was demonstrated in the study auditing.

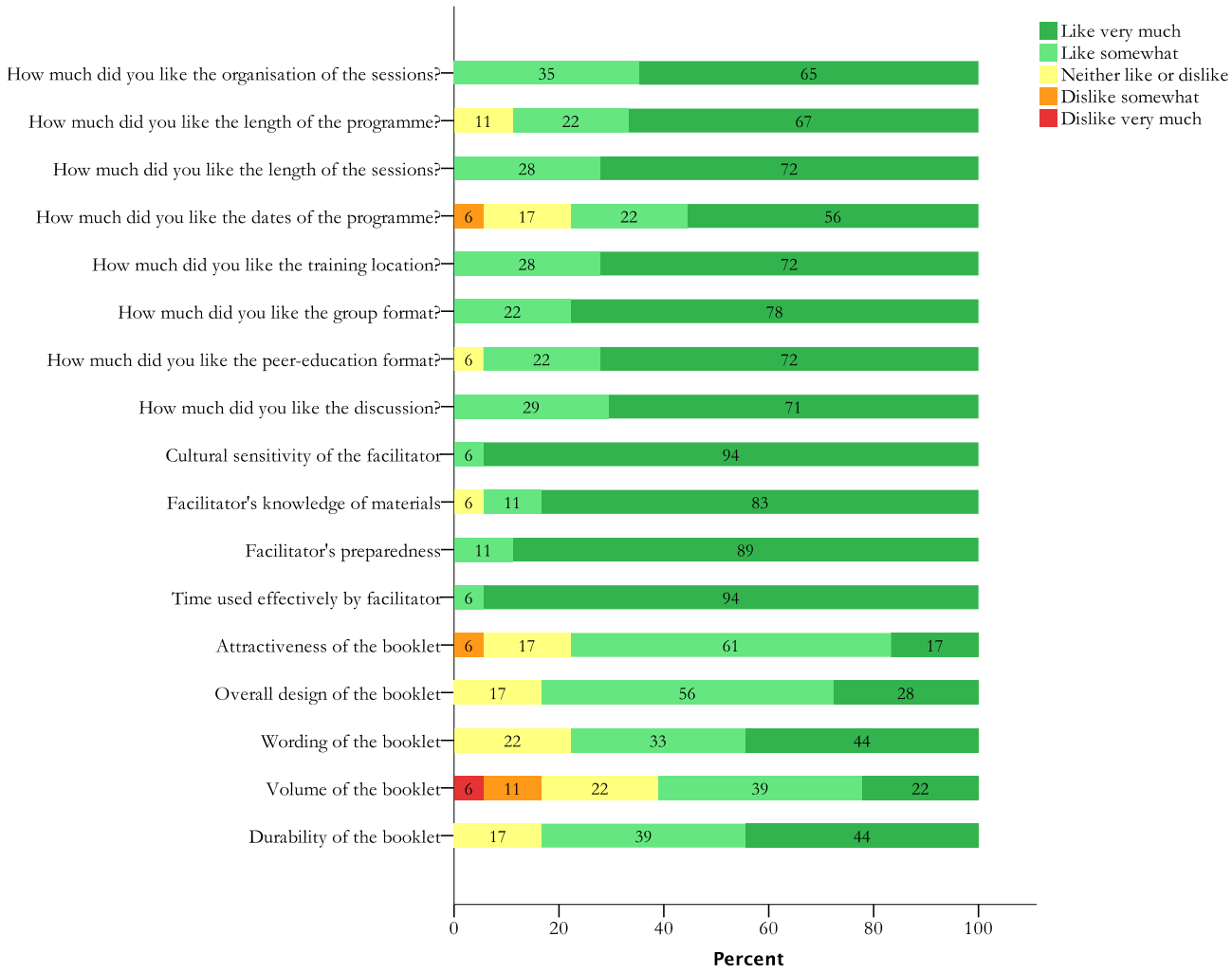

Figure 8.7 Percentage program satisfaction (n=18)

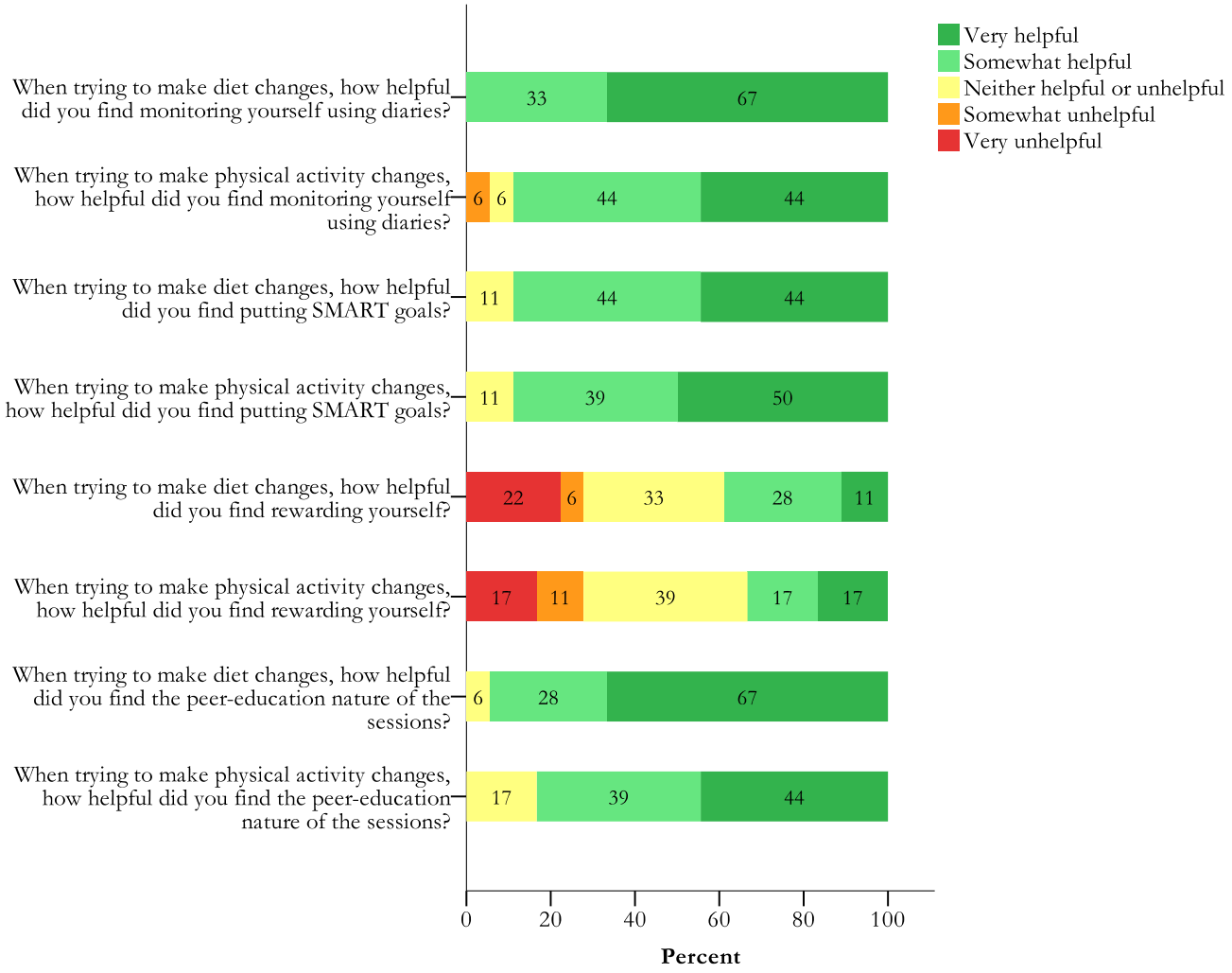

Figure 8.9 Helpfulness of BCTs in dietary and physical activity changes (n=18)

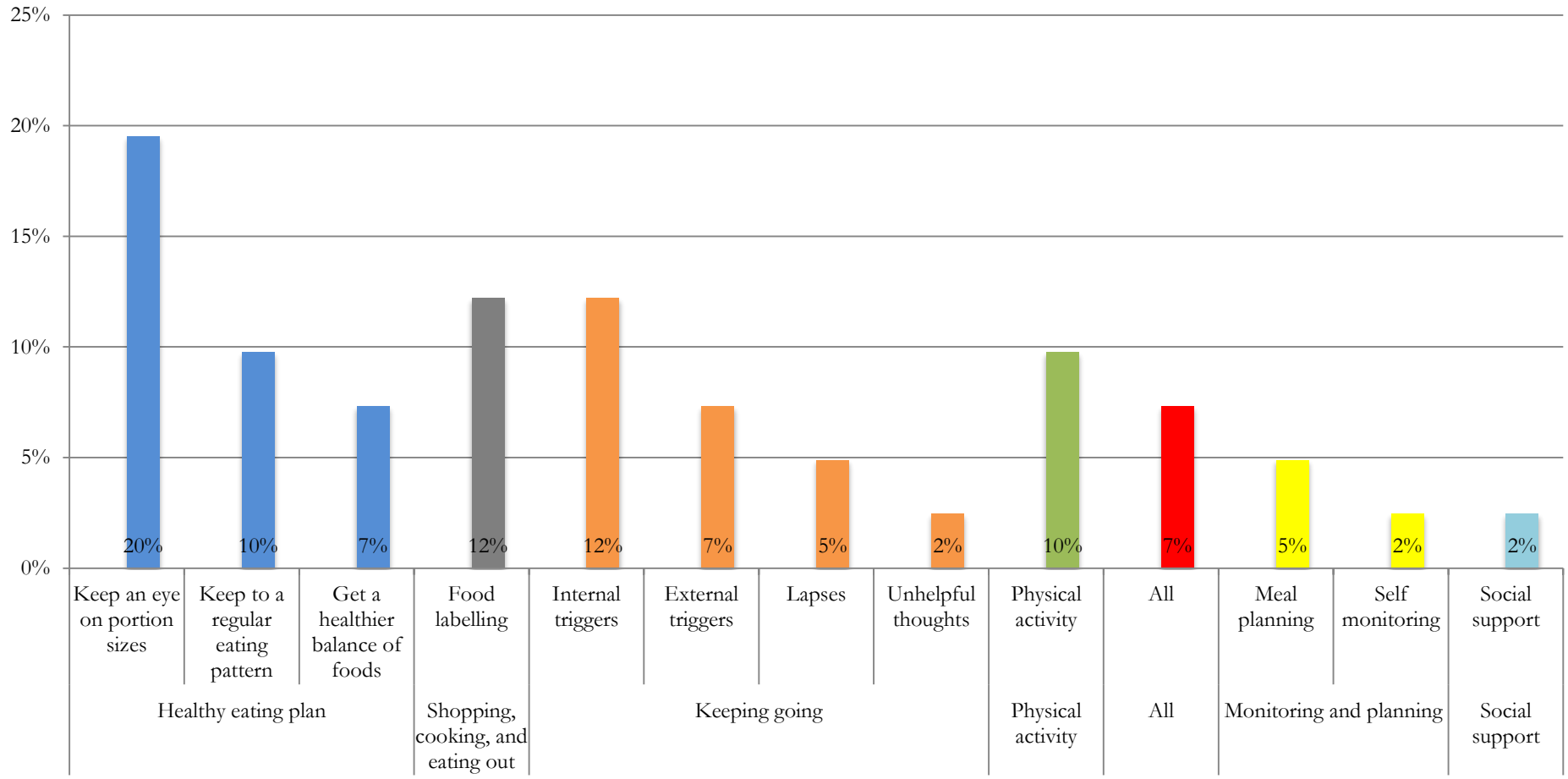

Figure 8.10 Percentage responses to the question "Which topic of the programme did you find the most useful?" by topic and programme section (in colour)

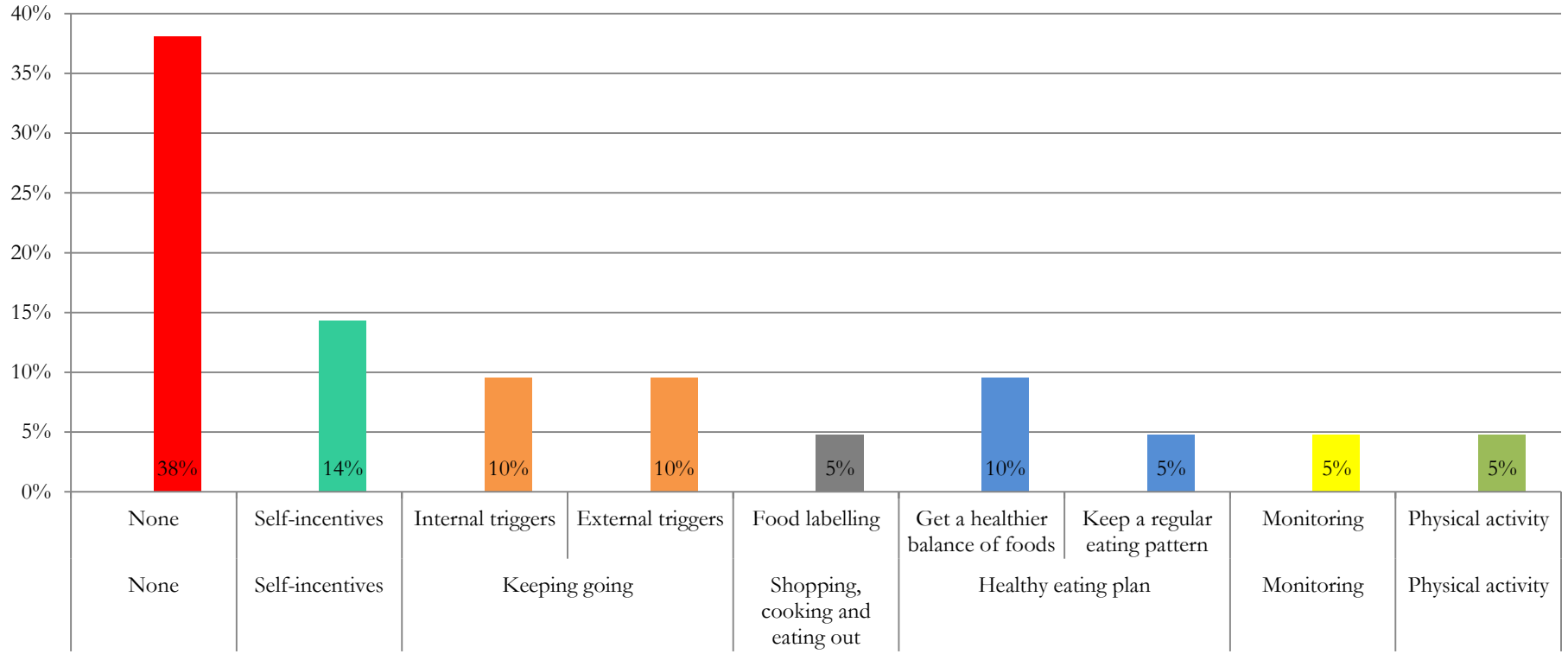

Figure 8.11 Percentage responses to the question "Which topic of the programme did you find the least useful?" by topic and programme section (in colour)

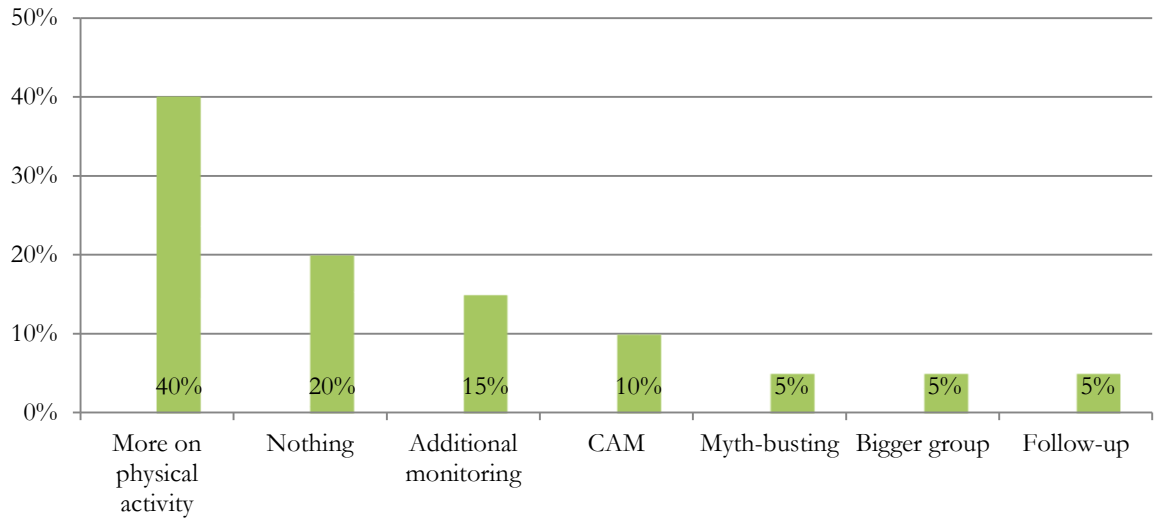

Figure 8.12 Percentage responses for potential additions to the program (CAM: Complementary and alternative medicine)

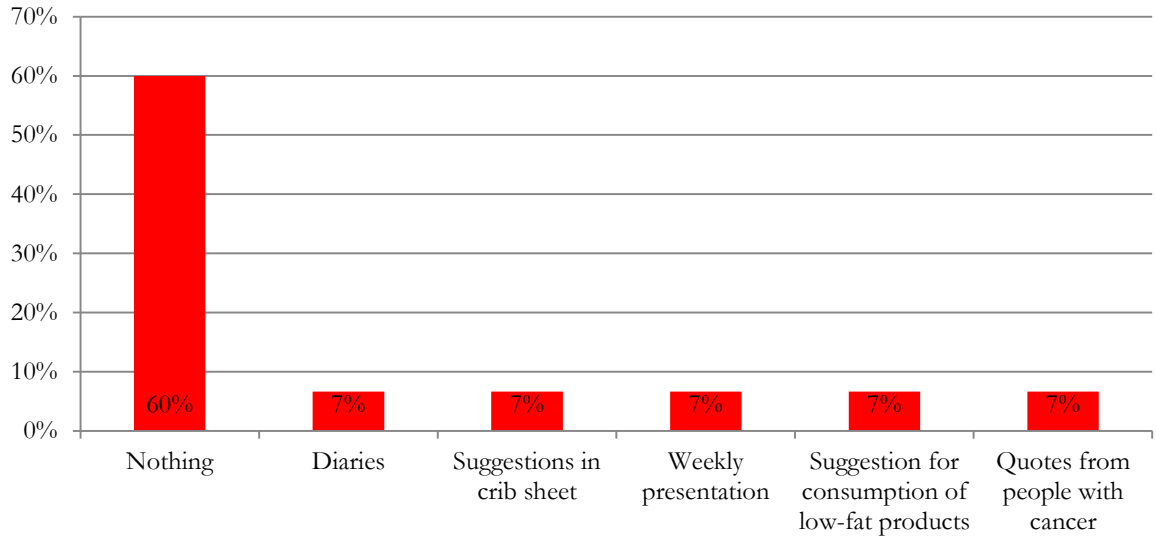

Figure 8.13 Percentage responses for program topics of potential elimination

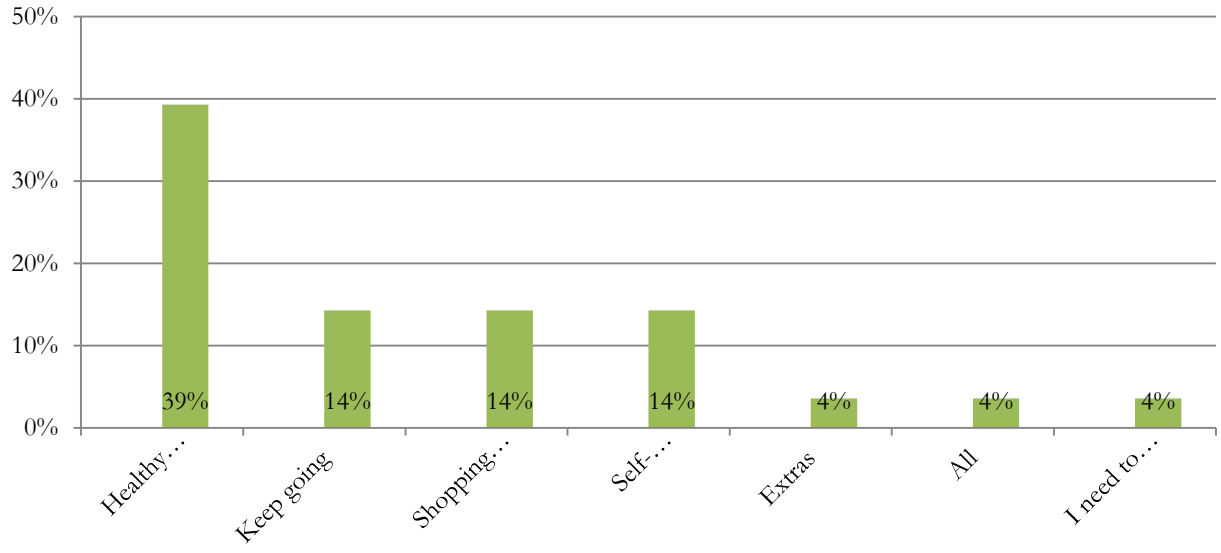

Figure 8.14 Percentage responses to the questions "Which one section of the booklet did you find most useful?"

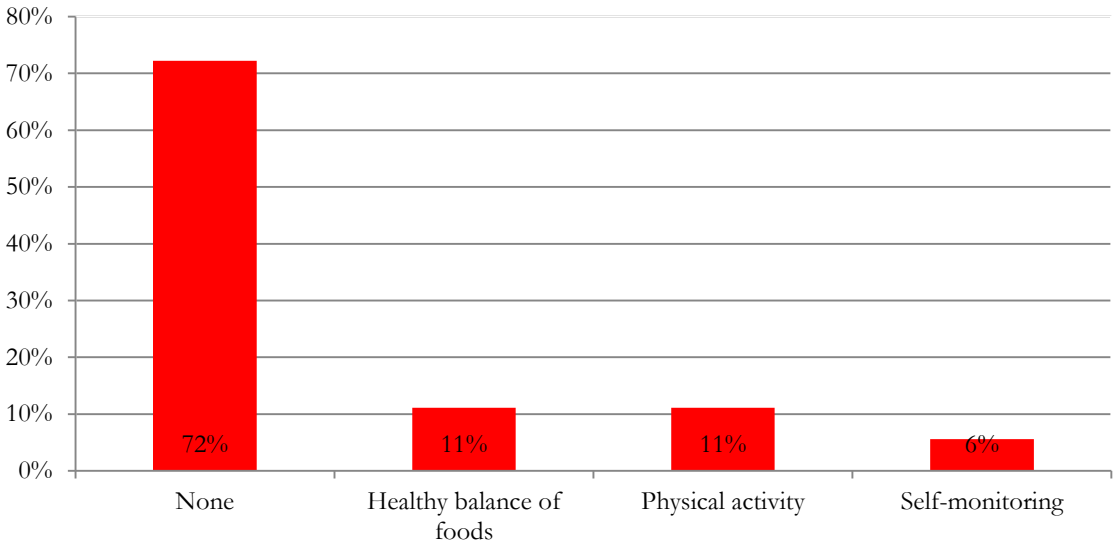

Figure 8.15 Percentage responses to the question "Which one section of the booklet did you find least useful?"

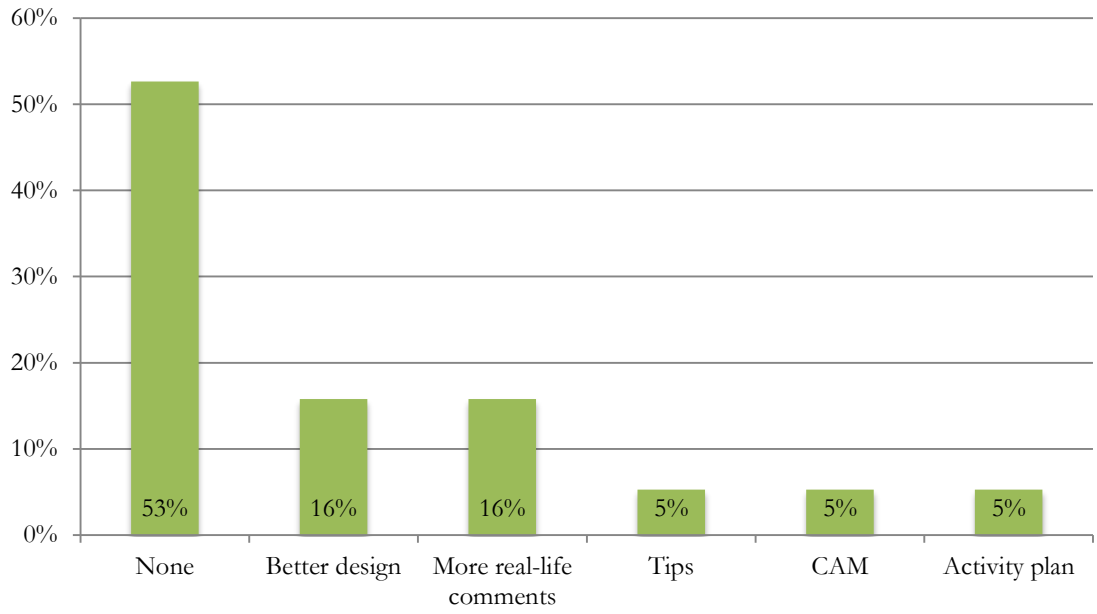

Figure 8.16 Percentage responses for potential additions to the booklet

CAM: Complementary and alternative medicine

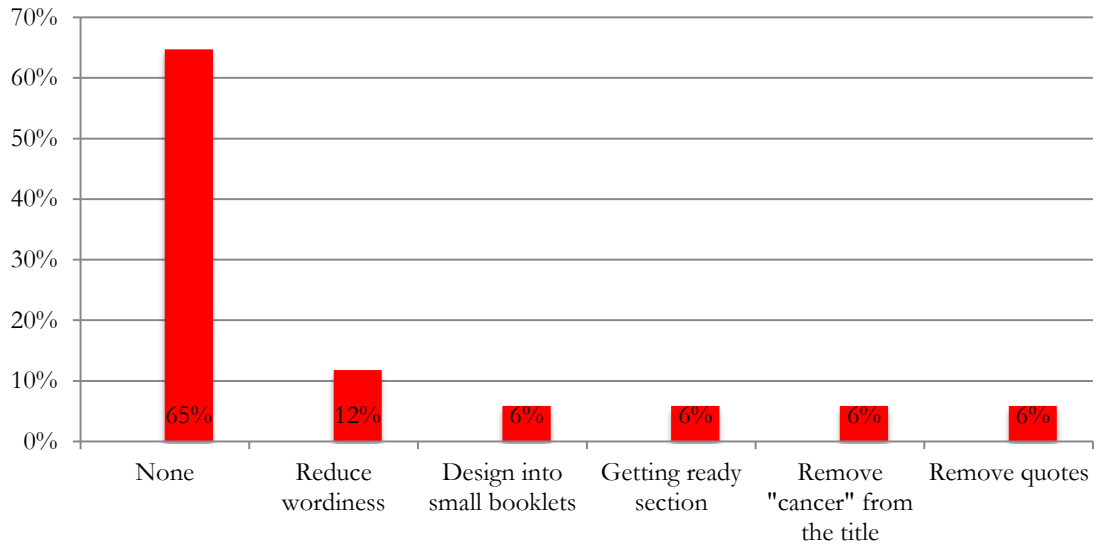

Figure 8.17 Percentage responses for topics of potential elimination in the booklet

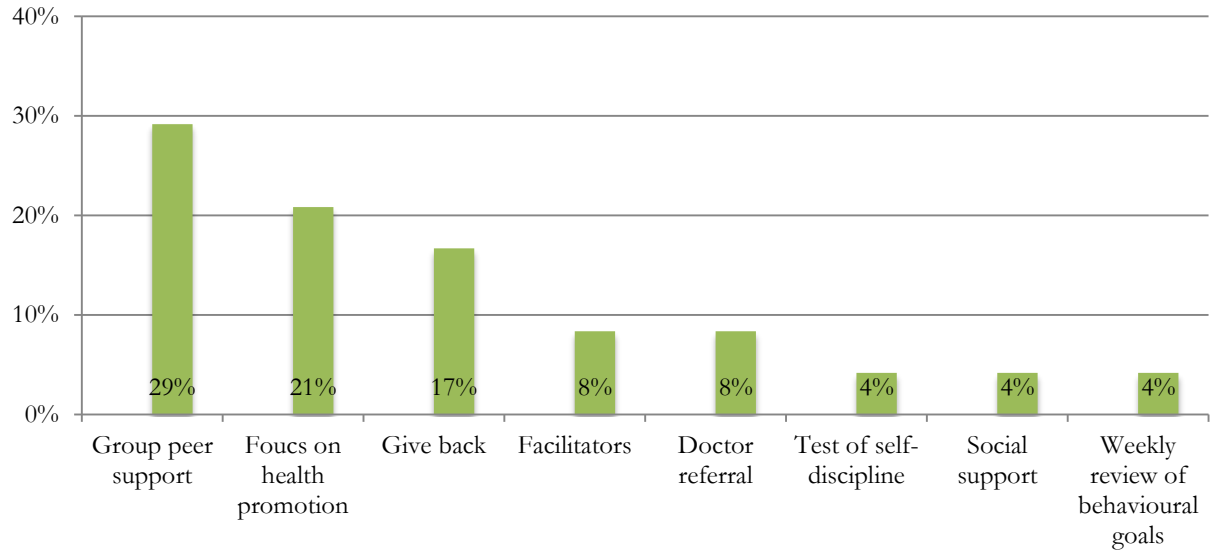

Figure 8.18 Percentage responses to the question "What helped you to be involved in the program?"

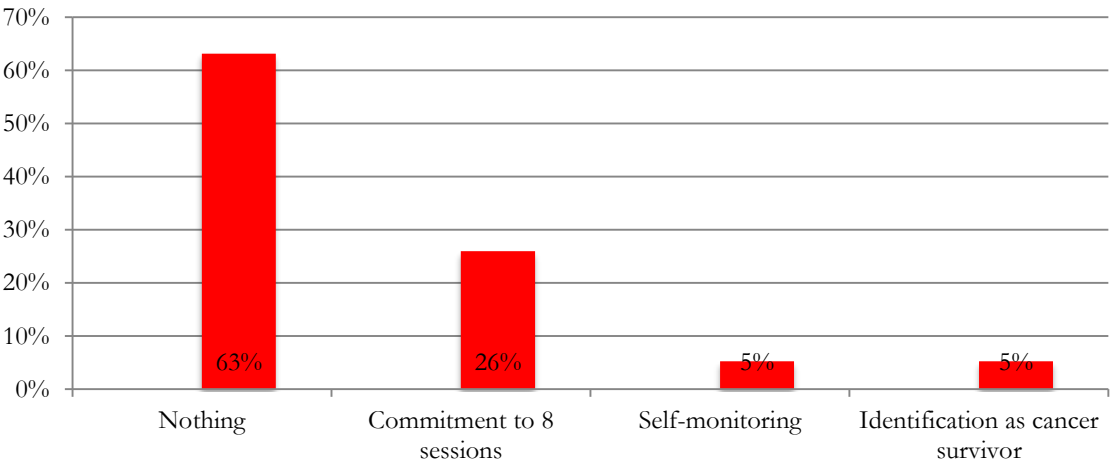

Figure 8.19 Percentage responses to the question "What discouraged you from getting involved in the program?"

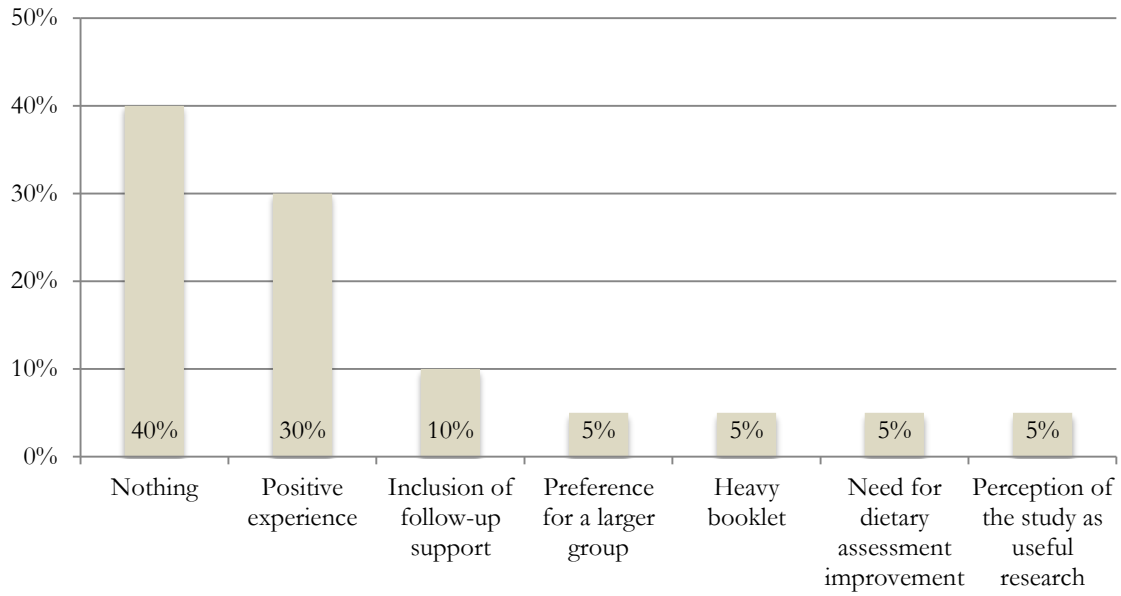

Figure 8.20 Percentage responses for additional comments

8.6.7 Retention

Retention rate was 92% (95% CI: 85%, 100%) with 24/28 and 25/26 eligible participants in the control and intervention arm completing all assessments, respectively (P=0.61 for difference between proportions). This indicated absence of attrition bias and the rejection of the null hypothesis that retention rate would be less than 60%.

8.6.8 Control arm contamination

Nine control arm participants (37.5%) searched for information on diet or physical activity. Two of them spoke with their GP, one with their nurse. Internet sources of information included the WCRF website (one), CRUK website (one), NHS choices (three), Change4Life (one), and other (two). One participant signed up to aerobic/tai chi classes. Two of them joined Slimming World; two weeks and one month before the final study

follow-up, respectively, achieving 5% and 7.5% weight loss compared to their 8-week measurements.

8.6.9 Harms

In the intervention arm, one participant reported fatigue during the intervention and another reported a fractured bone after intervention completion. None were related to the intervention. Five participants in the control arm reported adverse events (ovarian cancer diagnosis, cancer recurrence, bowel obstruction, fractured bone, and swollen ankle). One unrelated severe adverse event (death) occurred to a non-eligible participant randomised to the intervention arm. The direct cause of death was metastatic bronchial carcinoma. Other significant conditions leading to death were obstructive sleep apnoea and obesity hypoventilation syndrome. The participant withdrew due to medical reasons before commencement of the group sessions and, thus, the death was unrelated to the intervention. No safety concerns or complaints were reported.

8.6.10 Diet and self-efficacy

In the fully adjusted model, there was a statistical significant improvement in the overall AHEI-2010 score in the active intervention group at 8 weeks ($F(1, 44)=4.21$, $p=0.046$, partial $\eta^2= 0.087$) but not at 24 weeks ($F(1, 44)=0.002$, $p=0.964$, partial $\eta^2= 0.000046$). There was no evidence of statistically significant changes in vegetable or sodium scores (Table 8.6). With the exception of improvements in fruit intake that accounted for most of the overall AHEI positive change at 8-weeks, the change in the remaining index components was generally consistent. Furthermore, the relatively high self-efficacy score at baseline (Cronbach's alpha=0.77) did not change significantly between arms at follow-up.

8.6.11 Physical activity

The majority of participants (92.6%) were meeting the recommendations of at least 500 MET-minutes of moderate to vigorous physical activity at baseline. Moreover, 31.5% were also meeting at least 500 MET-minutes of vigorous physical activity at baseline. There was no evidence of a difference in the total energy expenditure or the energy expenditure from moderate to vigorous physical activities between groups at each time point (Table 8.6). Most participants did minimal strength and flexibility exercises throughout the study, with only some doing flexibility exercises particularly by attending yoga classes. The self-reported energy expenditure was significantly positively correlated both with estimated energy expenditure from ActivPal (r_s=0.42, p=0.03) and with step count (r_s=0.49, p=0.008). However, the Bland-Altman analysis (n=28) suggested that the questionnaire significantly overestimated total energy expenditure compared to ActivPal (mean difference=0.8 MET/h, 95% CI: -3.0, 4.7, p=0.03).

8.6.12 Anthropometry, body composition, blood pressure, hand-grip strength

Only 24.1% of participants (19.2% and 28.6% in the active intervention and usual care arm, respectively) were affected by obesity based on BMI. There was a statistically significant reduction in weight at 8weeks (F(1, 45)=1.73, p=0.196, partial η^2=0.153) but not at 24weeks (F(1, 43)=8.11, p=0.007, partial η^2=0.037) in the adjusted model. This observation was also evident for BMI. There was no evidence of significant changes in fat mass, muscle mass, fat mass index, fat free mass index. The mean systolic blood pressure was higher than the ideal 120mmHg value at baseline in each arm. In contrast, the mean diastolic blood pressure and handgrip strength were normal. No evidence of statistically significant differences between arms was obtained for these physical measurements, apart from handgrip strength at 24weeks (p=0.041). Time and group changes are presented in

Table 8.7 followed by ANCOVA statistics in Table 8.8. Figure 8.21 graphically demonstrates the change in weight, BMI, FMI, and FFMI. Individual changes in BMI are plotted in Figure 8.22 indicating potentially larger changes in those with BMI>25 compared to those with BMI<25.

Table 8.6 Arm means (SD) and differences between arm means for dietary, self-efficacy, and physical activity outcomes

	Mean (SD)						Active intervention minus usual care			
	Shape-Up FCT (n=25)			Care as usual (n=24)			Unadjusted Mean Group Difference at 8w (95% CI)	Adjusted Mean Group Difference at 8w (95% CI)	Unadjusted Mean Group Difference at 24w (95% CI)	Adjusted Mean Group Difference at 24w (95% CI)
Scores	Baseline	Change at 8w	Change at 24w	Baseline	Change at 8w	Change at 24w				
AHEI-2010	58.7 (12.6)	4.4 (15.3)	3.0 (14.0)	59.3 (15.4)	-2.9 (14.1)	2.2 (17.8)	7.4 (-0.7, 15.5)	7.5 (0.1, 14.9)*	1.0 (-8.3, 10.2)	0.2 (-7.7, 8.0)
Vegetables	3.6 (2.5)	0.4 (3.2)	0.1 (3.2)	4.2 (2.6)	-0.1 (4.0)	-0.6 (2.8)	-0.1 (-0.5, 0.4)	-0.3 (-1.9, 1.3)	0.2 (-1.2, 1.6)	0.4 (-1.0, 1.8)
Fruits	6.3 (3.5)	0.6 (3.9)	-0.3 (4.0)	4.9 (3.5)	-0.7 (3.0)	1.8 (4.2)	3.0 (1.0, 5.0)	-	-0.3 (-2.3, 1.7)	-
Whole grains	3.2 (3.6)	1.5 (4.4)	0.9 (3.8)	4.0 (3.5)	-1.0 (2.7)	-0.1 (3.8)	0.6 (0.0, 1.2)	-	0.6 (-1.5, 2.7)	-
SSBs & fruit juice	8.6 (3.4)	0.1 (4.4)	-0.4 (4.2)	7.8 (3.7)	0.1 (5.0)	1.1 (5.5)	-0.5 (-2.6, 1.5)	-	1.0 (-2.6, 1.5)	-
Nuts & legumes	4.1 (4.5)	0.6 (4.6)	0.0 (5.2)	4.7 (4.6)	-0.9 (6.0)	-0.9 (5.7)	1.1 (-1.6, 3.8)	-	1.3 (-2.3, 3.1)	-
Red & processed meat	8.5 (3.0)	-0.1 (4.5)	0.2 (3.1)	7.5 (3.4)	0.4 (4.6)	1.1 (4.9)	0.8 (-1.1, 2.6)	-	0.8 (-1.3, 2.0)	-
n-3 fatty acids	1.8 (3.5)	0.9 (4.6)	0.3 (4.2)	2.0 (3.7)	1.1 (4.3)	1.3 (4.6)	0.5 (0.1, 2.4)	-	1.2 (-3.6, 1.3)	-

	Mean (SD)						Active intervention minus usual care			
PUFA	5.1 (3.5)	1.0 (4.5)	0.1 (4.6)	5.5 (3.9)	-0.5 (4.1)	-0.5 (3.6)	-0.2 (-1.6, 1.3)	-	-0.1 (-1.9, 1.7)	-
trans fatty acids	9.8 (0.5)	-0.1 (0.9)	0.1 (0.6)	9.5 (0.7)	0.0 (0.8)	0.0 (1.1)	0.2 (-0.2, 0.6)	-	0.2 (-0.1, 0.8)	-
Alcohol	3.0 (2.4)	-0.2 (2.4)	1.5 (4.2)	4.0 (3.2)	-0.8 (2.8)	0.0 (1.7)	-1.0 (-2.4, 0.5)	-	1.0 (-2.0, 1.9)	-
Sodium	4.7 (3.1)	-0.3 (2.9)	0.5 (3.5)	5.1 (2.7)	-0.5 (3.1)	-1.0 (3.7)	0.8 (-0.9, 2.6)	-0.1 (-1.4, 1.3)	1.1 (-0.4, 2.6)	1.1 (-0.4, 2.6)
Shape-Up self-efficacy score[3]	3.6 (0.4)	0.2 (0.5)	0.1 (0.5)	3.6 (0.6)	-0.2 (0.7)	-0.1 (0.3)	0.3 (-0.1, 0.7)	0.3 (-0.1, 0.7)[4]	0.2 (-0.2, 0.5)	-
Total EE (MET-h/day)	35.1 (2.1)	-1.4 (2.2)	0.2 (2.1)	35.7 (2.9)	-1.8 (3.6)	0.4 (2.7)	-0.3 (-2.1, 1.6)	0.1 (-1.6 1.8)[1]	-0.2 (-2.1, 1.6)	0.1 (-1.1. 1.3)[2]
MVPA EE (MET-h/week)	32.7 (21.4)	6.5 (23.8)	3.3 (24.6)	40.7 (30.7)	3.5 (37.4)	1.7 (21.1)	-5.0 (-24.2, 14.1)	-	-6.4 (-22.4, 9.7)	-
	Median (IQR)									
Flexibility (min/day)	0.0 (0.2)	0.0 (4.8)	0.0 (35.1)	0.0 (2.1)	0.0 (3.2)	0.0 (24.3)	-	-	-	-
Strength (min/day)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.7)	-	-	-	-

SSBs: Sugar-sweetened beverages, EE: Energy expenditure, MET: Metabolic equivalents, MVPA: Moderate to vigorous physical activity, IQR: Interquartile range. FCT: following cancer treatment.

[1]Age was not included in this model as covariate because the linearity assumption was not met. [2]BMI was log transformed for this model. [3]n=23 for active intervention.

[4]BMI was not included in this model as covariate because the linearity assumption was not met.

Optimal potential AHEI-2010 score=110. Optimal potential score for each AHEI-2010 dietary component=10.

MVPA guidelines ≥8.3-16.7 MET-hours per week. Self-efficacy optimal potential score=5. *p<0.05

Table 8.7 Arm means (SD) in each odd row, medians (IQR) in each even row, and differences between arm means for anthropometry, body composition, blood pressure, and handgrip strength

	Each 1st row: Mean (SD), each 2nd row: Median (IQR)						Active intervention minus usual care			
	Shape-Up FCT (n=25)			Care as usual (n=24)			Unadjusted Mean Group Difference at 8w (95% CI)	Adjusted Mean Group Difference at 8w (95% CI)	Unadjusted Mean Group Difference at 24w (95% CI)	Adjusted Mean Group Difference at 24w (95% CI)
	Baseline	Change at 8w	Change at 24w	Baseline	Change at 8w	Change at 24w				
Weight (kg)	69.8 (14.8)	-0.9 (1.4)	-1.1 (2.6)	71.9 (15.2)	0.3 (1.5)	-0.2 (2.5)	-3.3 (-12.0, 5.3)	-1.2 (-2.0, -0.3)**	-3.0 (-11.3, 5.3)	-0.9 (-2.4, 0.5)
	66.5 (20.6)	-0.6 (1.4)	-0.6 (2.9)	69.4 (16.6)	0.2 (2.0)	0.4 (2.5)				
BMI (kg/m^2)	27.3 (6.5)	-0.4 (0.5)	-0.4 (1.0)	28.8 (6.1)	0.1 (0.6)	-0.1 (1.0)	-1.9 (-5.5, 1.7)	-0.5 (-0.8, -0.1)**	-1.8 (-5.3, 1.7)	-0.4 (-0.9, 0.2)
	26.2 (7.1)	-0.3 (0.5)	-0.2 (1.2)	26.9 (8.1)	0.1 (0.8)	0.2 (1.0)				
Fat mass (kg)	25.5 (10.1)	-0.3 (1.9)	-1.1 (2.1)	27.4 (10.3)	0.2 (1.3)	-0.5 (2.1)	-2.3 (-8.1, 3.5)	-0.6 (-1.5, 0.3)	-2.4 (-8.0, 3.2)	-0.7 (-1.9, 0.4)
	25.5 (14.1)	-0.6 (1.6)	-0.8 (2.6)	23.3 (12.3)	0.5 (1.6)	0.1 (1.8)				
Muscle mass (kg)	42.0 (5.4)	-0.5 (1.6)	0.1 (1.2)	42.3 (5.7)	0.0 (1.2)	0.3 (1.1)	-0.9 (-4.3, 2.5)	-0.5 (-1.3. 0.3)	-0.6 (-3.8, 2.7)	-0.2 (-0.8, 0.4)
	41.7 (6.9)	-0.5 (1.6)	0.3 (1.8)	40.9 (7.0)	-0.4 (2.0)	0.4 (1.9)				
FMI (kg/m^2)	10.0 (4.3)	-0.1 (0.8)	-0.4 (0.8)	10.9 (4.2)	0.1 (0.5)	-0.2 (0.8)	-1.1 (-3.5, 1.3)	-0.2 (-0.6, 0.1)	-1.1 (-3.5, 1.2)	-0.3 (-0.7, 0.2)
	9.3 (5.2)	-0.2 (0.8)	-0.3 (1.0)	9.7 (5.7)	0.2 (0.7)	0.0 (0.7)				
FFMI (kg/m^2)	17.3 (2.6)	-0.2 (0.6)	0.0 (0.5)	17.8 (2.2)	0.0 (0.5)	0.1 (0.5)	-0.7 (-2.2, 0.7)	-0.2 (-0.5, 0.1)[1]	-0.6 (-2.0, 0.8)	-0.1 (-0.4, 0.2)[1]
	16.7 (2.2)	-0.2 (0.7)	0.1 (0.8)	16.8 (3.3)	-0.2 (0.7)	0.2 (0.8)				
Systolic blood pressure (mmHg)	142.9 (27.8)	-7.9 (16.6)	-11.1 (14.9)	139.7 (15.5)	0.7 (20.4)	-8.0 (10.7)	-5.5 (-21.0, 10.1)	-6.3 (-16.1, 3.6)	0.1 (-10.9, 11.0)	-1.9 (-8.3, 4.5)
	128.5 (50.5)	-5.0 (16.0)	-9.5 (15.0)	141.0 (19.5)	-0.3 (26.8)	-9.0 (13.0)				

	Each 1st row: Mean (SD), each 2nd row: Median (IQR)						Active intervention minus usual care			
Diastolic blood pressure (mmHg)	80.2 (7.4)	-1.9 (6.1)	-5.4 (5.6)	79.3 (9.0)	3.3 (9.8)	-3.3 (5.5)	-4.3 (-10.2, 1.7)	-	-1.2 (-6.3, 3.8)	-2.1 (-5.3, 1.1)
	79.5 (7.0)	-2.5 (7.0)	-4.0 (7.5)	77.0 (11.3)	1.3 (11.8)	-5.0 (6.8)				
Hand grip strength (kg))	22.5 (4.4)	-0.3 (2.4)	0.0 (2.4)	23.1 (4.0)	-1.7 (3.1)	-1.3 (1.9)	0.8 (-2.1, 3.8)	1.5 (-0.1. 3.1)[2]	0.7 (-1.8, 3.1)	1.3 (0.1, 2.5)[2]*
	23.8 (5.7)	0.3 (3.3)	0.3 (2.4)	22.8 (7.3)	-1.4 (2.8)	-1.4 (2.2)				

FMI: Fat mass index, FFMI: Fat free mass index. BMI was not included as covariate in the models for weight, fat mass, fat free mass, FMI, FFMI.

[1]Only baseline FFMI was included as covariate in this model because the linearity assumption was not met for age.

[2]BMI was not included in this model as covariate because the linearity assumption was not met. *p<0.05, **p<0.01

Table 8.8 F-distributions, P-values, and partial η-squared from ANCOVAs for body composition and physical measurements

	8-weeks			24-weeks		
	F (df)	*P*-value	Partial η^2	F (df)	*P*-value	Partial η^2
BMI	F(1, 45)=8.163	0.006	0.154	F(1, 45)=1.822	0.184	0.039
Fat mass	(F(1, 44)=1.684	0.201	0.037	(F(1, 44)=1.577	0.219	0.034
Muscle mass	(F(1, 44)=1.567	0.217	0.034	F(1, 44)=0.356	0.554	0.008
FMI	F(1, 44)=1.592	0.214	0.035	F(1, 44)=1.512	0.225	0.033
FFMI	F(1, 45)=1.721	0.196	0.037	F(1, 45)=0.808	0.374	0.018
SBP	F(1, 44)=1.645	0.206	0.036	F(1, 44)=0.363	0.550	0.008
DBP	No ANCOVA performed			F(1, 41)= 1.825	0.184	0.040
HGS	F(1, 45)= 3.647	0.063	0.075	F(1, 45)= 4.418	0.041	0.089

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HGS: Handgrip strength

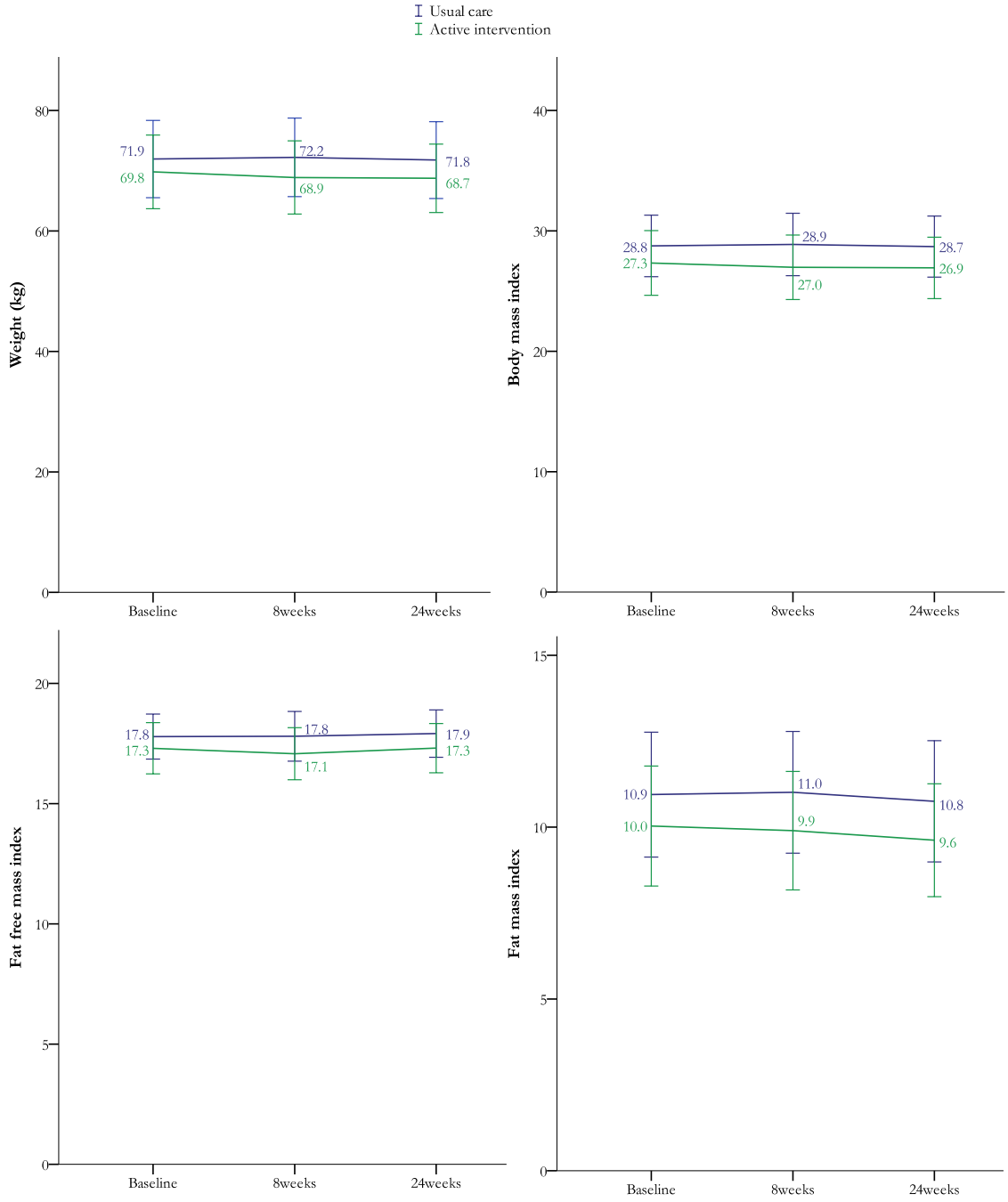

Figure 8.21 Mean (95% CI) weight, BMI, and body composition in each arm at each time point

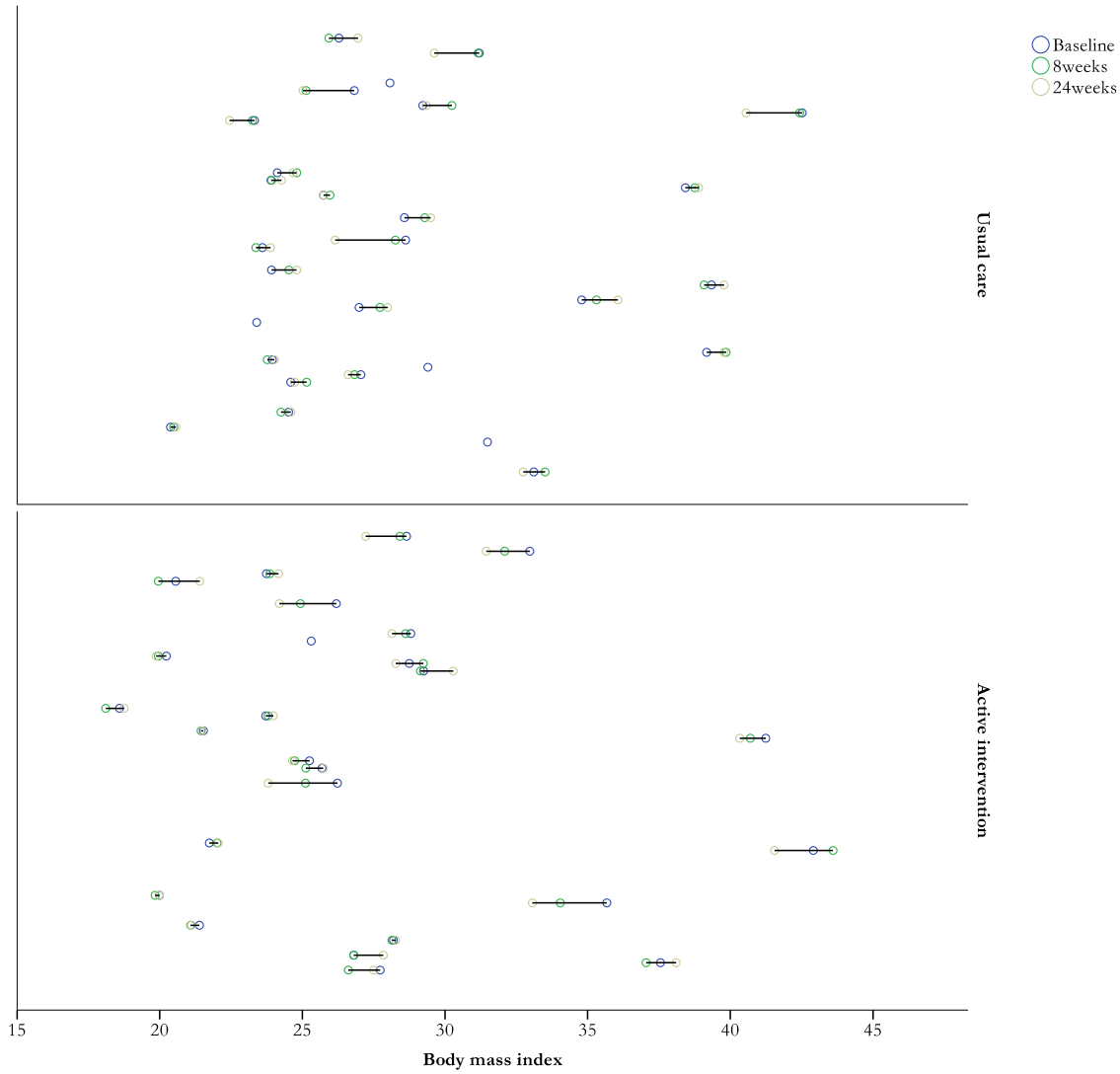

Figure 8.22 BMI changes for each participant

8.6.13 HRQoL

HRQoL scores, function scale scores, and symptom scores are presented in Table 8.9 for both arms with their changes at each time point. These are also illustrated in Figure 8.23, Figure 8.24, Figure 8.25, and Figure 8.26. Overall, the baseline scores were high for the functional scales and low for the symptoms, except fatigue, insomnia, and muscular pain.

In the adjusted model, there was no statistically significant difference in the global HRQoL between interventions at 8 weeks (F(1, 44)=0.415, p=0.523, partial η^2=0.009) or 24 weeks (F(1, 43)=1.137, p=0.292, partial η^2=0.025). The same applied for the overall health score at 8 weeks (F(1, 44)=1.152, p=0.289, partial η^2=0.026). Overall health score at 24-weeks was significantly higher in the active intervention group (F(1, 46)=5.69, p=0.021, partial η^2=0.11).

Physical function did not differ between groups at 8-weeks (F(1, 44)=3.6, p=0.064, partial η^2=0.076). It also did not differ significantly at 24-weeks (F(1, 44)=0.263, p=0.611, partial η^2=0.006). Regarding fatigue, both 8-week and 24-week scores were not statistically different from baseline (F(1, 43)=1.579, p=0.216, partial η^2=0.035 and F(1, 42)=2.144, p=0.151, partial η^2=0.049, respectively). Similar non-significant estimates were found for insomnia (F(1, 44)=0.942, p=0.337, partial η^2=0.021 at 8weeks and F(1, 44)=0.119, p=0.732, partial η^2=0.003 at 24weeks).

Among all other symptoms, only constipation significantly improved at 8-weeks (p=0.03) in the unadjusted model. Regarding the items specific to endometrial cancer, there was no observed significant change for all scales but a significant improvement in the gastrointestinal symptoms at 8-weeks (p=0.02) in the unadjusted model (Table 8.10).

Table 8.9 Arm means (SD) in each odd row, medians (IQR) in each even row, and differences between arm means for general HRQoL outcomes

	Each 1st row: Mean (SD), each 2nd row: Median (IQR)						Active intervention minus usual care			
	Shape-Up FCT (n=25)			Care as usual (n=24)			Unadjusted Mean Group Difference at 8w (95% CI)	Adjusted Mean Group Difference at 8w (95% CI)	Unadjusted Mean Group Difference at 24w (95% CI)	Adjusted Mean Group Difference at 24w (95% CI)
	Baseline	Change at 8w	Change at 24w	Baseline	Change at 8w	Change at 24w				
Global Quality of Life	73.3 (16.0)	0.7 (17.7)	7.3 (16.7)	75.0 (22.0)	-3.5 (19.0)	1.4 (19.6)	2.5 (-8.3, 13.3)	3.1 (-6.5, 12.6)	4.3 (-5.5, 14.1)	4.6 (-4.1, 13.4)[1]
	83.3 (16.7)	0.0 (33.3)	0.0 (16.7)	66.7 (33.3)	0.0 (25.0)	0.0 (33.3)				
Overall Health	68.0 (14.4)	5.3 (12.5)	10.0 (16.0)	73.6 (18.3)	-2.8 (20.1)	-4.2 (21.0)	2.5 (-9.1, 14.1)	5.2 (-4.5, 14.9)	8.6 (-3.8, 21.0)	12.6 (2.0, 23.2)[2]*
	66.7 (16.7)	0.0 (16.7)	16.7 (16.7)	75.0 (16.7)	0.0 (8.3)	0.0 (16.7)				
Physical functioning	89.6 (12.0)	2.4 (9.4)	1.6 (9.3)	91.1 (15.1)	-2.3 (7.4)	0.3 (6.4)	3.3 (-4.7, 11.3)	4.5 (-0.3, 9.4)[3]	-0.2 (-7.4, 7.0)	1.1 (-3.0, 5.1)
	93.3 (13.3)	0.0 (6.7)	0.0 (6.7)	93.3 (6.7)	0.0 (6.7)	0.0 (6.7)				
Role functioning	88.7 (15.0)	-1.3 (24.5)	2.7 (19.6)	93.1 (12.9)	-7.6 (26.0)	-6.3 (20.2)	1.9 (-10.5, 14.4)	-	4.5 (-6.1, 15.2)	-
	100.0 (16.7)	0.0 (33.3)	0.0 (16.7)	100.0 (16.7)	0.0 (0.0)	0.0 (8.3)				
Emotional functioning	78.3 (22.4)	4.0 (20.3)	9.0 (18.9)	82.2 (20.0)	-2.8 (14.5)	0.4 (9.6)	1.7 (-9.2, 12.5)	-	5.0 (-4.4, 14.5)	-
	91.7 (33.3)	0.0 (25.0)	0.0 (25.0)	83.3 (25.0)	0.0 (16.7)	0.0 (16.7)				
Cognitive functioning	83.3 (12.7)	3.3 (16.7)	7.3 (16.0)	86.8 (13.9)	-2.8 (16.8)	1.4 (9.9)	2.6 (-7.9, 13.2)	-	2.3 (-5.2, 9.7)	-
	83.3 (33.3)	0.0 (16.7)	0.0 (16.7)	83.3 (16.7)	0.0 (8.3)	0.0 (0.0)				
Social functioning	88.7 (17.8)	2.7 (15.0)	6.7 (18.0)	86.1 (20.1)	3.5 (18.4)	6.3 (15.4)	1.8 (-6.9, 10.4)	-	3.0 (-4.8, 10.8)	-
	100.0 (16.7)	0.0 (16.7)	0.0 (0.0)	100.0 (25.0)	0.0 (0.0)	0.0 (16.7)				

	Each 1st row: Mean (SD), each 2nd row: Median (IQR)						Active intervention minus usual care			
Fatigue[4]	19.6 (13.3) 22.2 (11.1)	-.9 (19.2) -11.1 (22.2)	-5.1 (16.7) -11.1 (11.1)	18.8 (16.9) 22.2 (33.3)	8.2 (20.4) 11.1 (33.3)	2.9 (15.4) 0.0 (22.2)	-8.2 (-20.3, 3.9)	-6.8 (-17.8, 4.1)	-6.0 (-15.5, 3.5)	-6.2 (-14.8, 2.3)
Pain	20.7 (26.9) 16.7 (33.3)	-4.7 (15.6) 0.0 (16.7)	-6.7 (21.5) 0.0 (16.7)	10.4 (15.4) 0.0 (16.7)	6.3 (21.3) 0.0 (8.3)	6.3 (21.9) 0.0 (8.3)	-0.7 (-12.8, 11.4)	-	-2.7 (-15.3, 9.9)	-
Nausea and vomiting	3.3 (8.3) 0.0 (0.0)	8.7 (30.5) 0.0 (0.0)	-1.3 (4.6) 0.0 (0.0)	2.1 (5.6) 0.0 (0.0)	1.4 (10.9) 0.0 (0.0)	-1.4 (4.7) 0.0 (0.0)	8.5 (-3.9, 21.0)	-	1.3 (-2.0, 4.6)	-
Dyspnoea	6.7 (13.6) 0.0 (0.0)	0.0 (13.6) 0.0 (0.0)	-4.0 (17.5) 0.0 (0.0)	15.3 (21.9) 0.0 (33.3)	0.0 (17.0) 0.0 (0.0)	-2.8 (16.8) 0.0 (0.0)	-8.6 (-20.7, 3.5)	-	-9.8 (-20.4, 0.7)	-
Insomnia	32.0 (28.0) 33.3 (33.3)	-5.3 (26.7) 0.0 (33.3)	-12.0 (27.0) 0.0 (33.3)	40.3 (35.4) 33.3 (66.7)	-1.4 (30.3) 0.0 (50.0)	-12.5 (35.2) 0.0 (33.3)	-12.2 (-28.8, 4.4)	-6.6 (-20.3. 7.1)	-7.8 (-24.4, 8.8)	-2.5 (-17.1, 12.1)
Appetite loss	5.3 (20.8) 0.0 (0.0)	-1.3 (26.3) 0.0 (0.0)	0.0 (27.2) 0.0 (0.0)	4.2 (11.3) 0.0 (0.0)	0.0 (9.8) 0.0 (0.0)	-1.4 (12.0) 0.0 (0.0)	-0.2 (-7.7, 7.4)	-	2.6 (-4.9, 10.1)	-
Constipation	2.7 (9.2) 0.0 (0.0)	0.0 (9.6) 0.0 (0.0)	0.0 (13.6) 0.0 (0.0)	12.5 (25.7) 0.0 (16.7)	5.6 (25.4) 0.0 (0.0)	-1.4 (23.0) 0.0 (0.0)	-15.4 (-29.6, -1.2)	-	-8.4 (-19.7, 2.8)	-
Diarrhoea	1.3 (6.7) 0.0 (0.0)	2.7 (13.3) 0.0 (0.0)	-1.3 (6.7) 0.0 (0.0)	4.2 (11.3) 0.0 (0.0)	-2.8 (9.4) 0.0 (0.0)	0.0 (17.0) 0.0 (0.0)	2.6 (-2.7, 7.9)	-	-4.2 (-10.5, 2.1)	-
Financial difficulties	6.7 (16.7) 0.0 (0.0)	-2.7 (9.2) 0.0 (0.0)	-4.0 (17.5) 0.0 (0.0)	2.8 (9.4) 0.0 (0.0)	0.0 (9.8) 0.0 (0.0)	-1.4 (6.8) 0.0 (0.0)	1.2 (-4.7, 7.1)	-	1.3 (-3.4, 6.0)	-

Each 1st row: Mean (SD), each 2nd row: Median (IQR)		Active intervention minus usual care

Higher scores in QoL and functioning scales indicate higher QoL and higher level of functioning, respectively. Higher scores in symptom scales indicate higher symptomatology.

[1]Age was not included in this model as covariate because the linearity assumption was not met.

[2]Only baseline overall health score was included as covariate in this model because the linearity assumption was not met for age and BMI.

[3]BMI was not included in this model as covariate because the linearity assumption was not met. [4]Usual care n=23 for both follow-ups, Active intervention n=24 for 24week.

Table 8.10 Arm means (SD) in each odd row, medians (IQR) in each even row, and differences between arm means for HRQoL outcomes specific to endometrial cancer (EORTC-QLQ-EN24)

	1st row: Mean (SD), 2nd row: Median (IQR)						Active intervention minus usual care			
	Shape-Up FCT (n=25)			Care as usual (n=24)			Unadjusted Mean Group Difference at 8w (95% CI)	Adjusted Mean Group Difference at 8w (95% CI)	Unadjusted Mean Group Difference at 24w (95% CI)	Adjusted Mean Group Difference at 24w (95% CI)
	Baseline	Change at 8w	Change at 24w	Baseline	Change at 8w	Change at 24w				
Sexual interest	21.3 (28.7)	0.0 (16.7)	1.4 (25.0)	30.4 (26.4)	-2.9 (19.9)	-2.9 (19.9)	-6.2	-	-3.9	-
	0.0 (33.3)	0.0 (0.0)	0.0 (0.0)	33.3 (66.7)	0.0 (0.0)	0.0 (0.0)	(-21.1, 8.7)		(-20.5, 12.7)	
Sexually active	16.7 (24.1)	0.0 (17.0)	-2.9 (17.2)	26.1 (26.5)	-5.8 (16.4)	-4.3 (18.3)	-3.0	-	-7.2	-
	0.0 (33.3)	0.0 (0.0)	0.0 (0.0)	33.3 (33.3)	0.0 (0.0)	0.0 (0.0)	(-16.3, 10.4)		(-20.9, 6.4)	
Sexual enjoyment	60.0 (26.3)	6.7 (14.1)	3.3 (29.2)	57.6 (21.6)	-3.0 (10.1)	-6.7 (14.1)	16.7	-	17.9	-
	66.7 (33.3)	0.0 (0.0)	0.0 (0.0)	66.7 (33.3)	0.0 (0.0)	0.0 (0.0)	(-6.1, 39.4)		(-5.8, 41.5)	
Lympoedema	8.7 (21.6)	0.7 (13.2)	-2.7 (11.5)	4.2 (8.9)	5.6 (16.1)	2.8 (12.7)	-0.4	-	-0.9	-
	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	(-10.1, 9.3)		(-10.8, 8.9)	
Urological symptoms	17.7 (17.1)	-3.5 (12.5)	-2.4 (14.6)	12.5 (12.8)	3.5 (16.3)	2.1 (9.9)	-1.6	-	0.1	-
	16.7 (16.7)	0.0 (12.5)	0.0 (8.3)	8.3 (20.8)	4.2 (20.8)	0.0 (16.7)	(-10.0, 6.7)		(-8.2, 8.4)	
GI symptoms	7.2 (8.1)	-2.7 (9.2)	-3.2 (8.2)	10.0 (9.0)	2.0 (9.7)	-4.2 (9.4)	-7.4	-	-1.8	-
	6.7 (13.3)	0.0 (6.7)	0.0 (6.7)	6.7 (13.3)	0.0 (13.3)	0.0 (10.0)	(-13.3, -1.4)		(-5.9, 2.2)	
Poor body image	8.7 (22.1)	-3.3 (14.4)	-6.0 (14.3)	11.8 (21.7)	1.4 (13.8)	-4.9 (17.4)	-7.9	-	-4.3	-
	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (16.7)	0.0 (0.0)	0.0 (0.0)	(-18.5, 2.8)		(-10.7, 2.2)	

	1st row: Mean (SD), 2nd row: Median (IQR)						Active intervention minus usual care			
Sexual/vaginal problems	25.6 (17.4) 27.8 (22.2)	1.1 (14.3) 0.0 (22.2)	-3.3 (16.6) -5.6 (11.1)	34.4 (32.5) 22.2 (55.6)	7.8 (16.6) 0.0 (22.2)	6.2 (14.8) 0.0 (11.1)	-13.5 (-36.5, 9.5)	-	-21.2 (-47.7, 5.3)	-
Pain in back & pelvis	18.7 (23.7) 0.0 (33.3)	-1.3 (20.4) 0.0 (0.0)	0.0 (19.2) 0.0 (0.0)	18.1 (24.0) 0.0 (33.3)	8.3 (28.2) 0.0 (33.3)	0.0 (29.5) 0.0 (0.0)	-9.1 (-23.9, 5.8)	-	0.6 (-13.1, 14.3)	-
Tingling / numbness	16.0 (29.1) 0.0 (33.3)	-6.7 (16.7) 0.0 (0.0)	-2.7 (25.3) 0.0 (0.0)	18.1 (27.8) 0.0 (33.3)	-2.8 (21.8) 0.0 (0.0)	-4.2 (14.9) 0.0 (0.0)	-5.9 (-19.3, 7.5)	-	-0.6 (-13.0, 11.9)	-
Muscular pain	36.0 (25.3) 33.3 (0.0)	-6.9 (26.0) 0.0 (33.3)	-8.0 (22.1) 0.0 (33.3)	20.8 (23.7) 16.7 (33.3)	1.4 (20.8) 0.0 (0.0)	4.2 (22.7) 0.0 (0.0)	5.6 (-10.3, 21.4)	-	3.0 (-11.8, 17.8)	-
Hair loss	10.7 (23.0) 0.0 (0.0)	-5.3 (18.5) 0.0 (0.0)	-2.7 (13.3) 0.0 (0.0)	8.3 (17.7) 0.0 (0.0)	1.4 (12.0) 0.0 (0.0)	2.8 (9.4) 0.0 (0.0)	-4.4 (-13.5, 4.7)	-	-3.1 (-13.5, 7.3)	-
Taste change	1.3 (6.7) 0.0 (0.0)	0.0 (9.6) 0.0 (0.0)	5.3 (18.5) 0.0 (0.0)	2.8 (9.4) 0.0 (0.0)	-2.8 (9.4) 0.0 (0.0)	-2.8 (9.4) 0.0 (0.0)	1.3 (-1.4, 4.1)	-	6.7 (-0.2, 13.5)	-

Higher scores in sexual functioning scales indicate higher level of functioning. Higher scores in symptom scales indicate higher symptomatology.
N=10 in each arm for the sexual enjoyment and sexual/vaginal problems. FCT: following cancer treatment

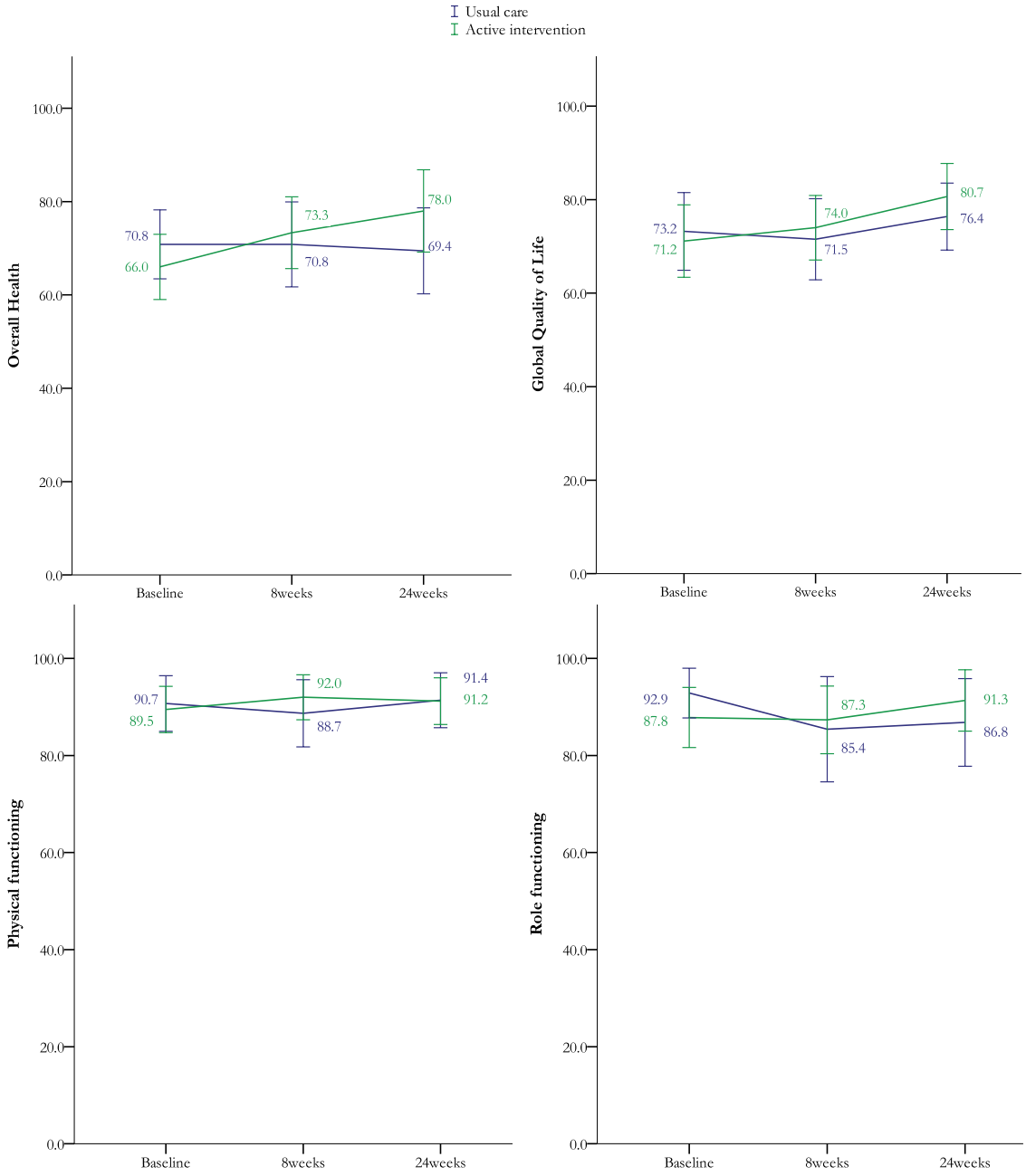

Figure 8.23 Mean (95% CI) overall health, QoL, physical and role functioning in each arm at each time point (n=49)

Higher scores indicate higher level of functioning/higher QoL.

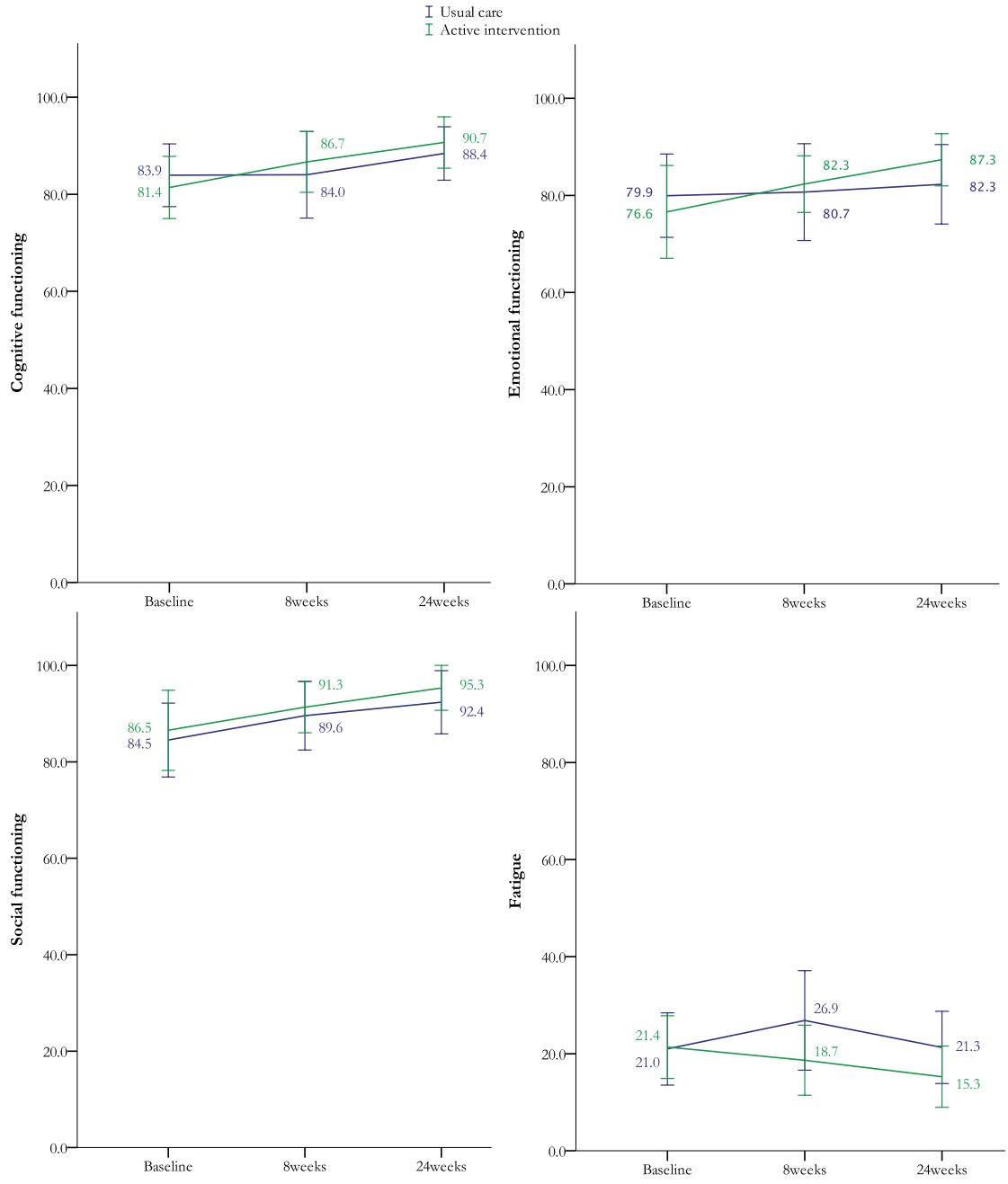

Figure 8.24 Mean (95% CI) for cognitive, emotional, and social functioning, and fatigue in each arm at each time point (n=49)

Higher scores in the functional scales indicate higher level of functioning/higher fatigue.

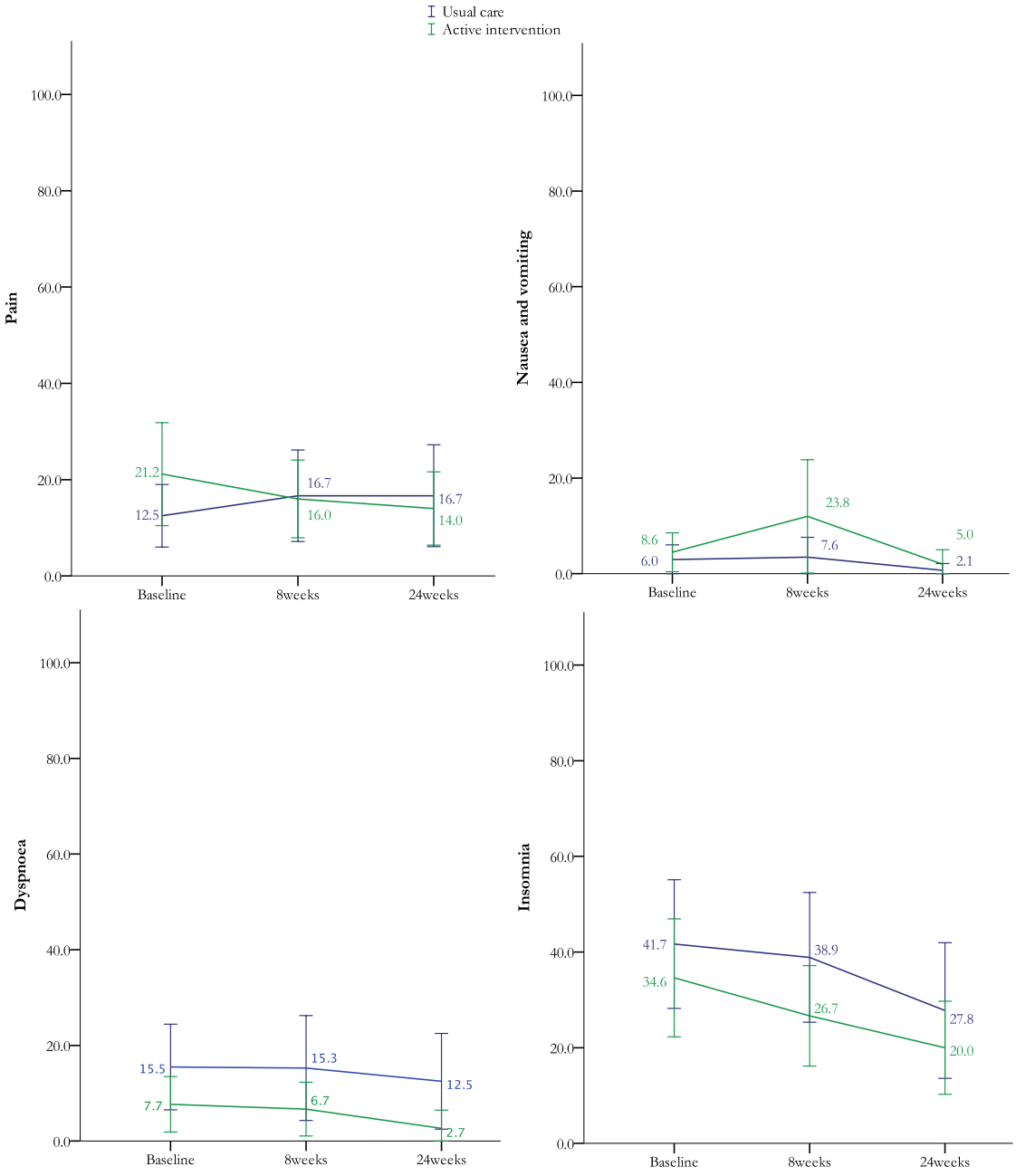

Figure 8.25 Mean (95% CI) for pain, nausea, dyspnoea, and insomnia in each arm at each time point (n=49)

Higher scores indicate higher symptomatology.

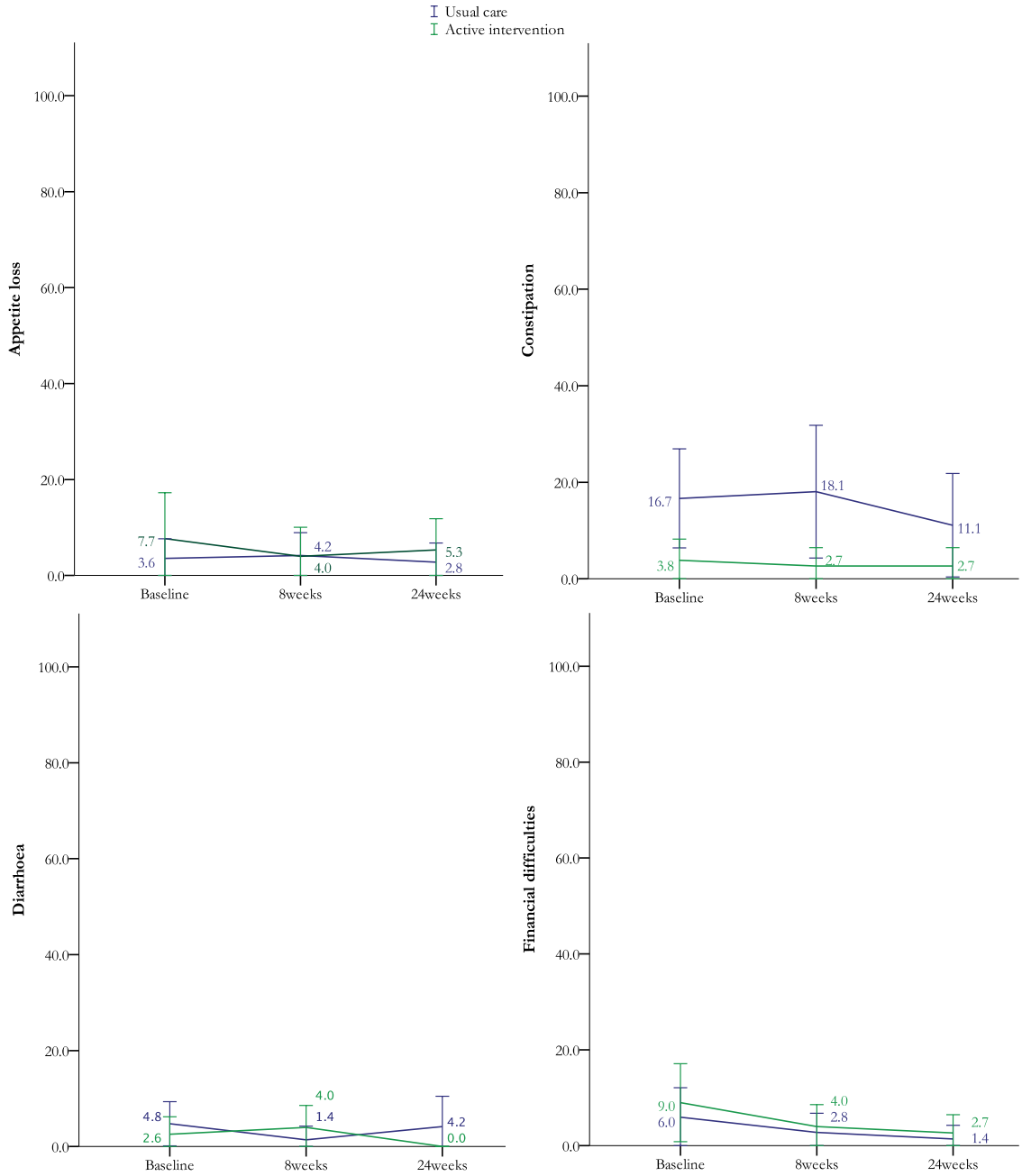

Figure 8.26 Mean (95% CI) for appetite loss, constipation, diarrhoea, and financial difficulties ine ach arm at each time point (n=49)

Higher scores indicate higher symptomatology/problems

8.6.14 Health care resource use and EQ-5D health state

Within the study period, participants reported a mean (SD) 1.4 (1.9) visits to their GP and 1.7 (1.6) visits to hospital outpatients, mainly in the oncology department (Table 8.11). There were no hospital admissions or use of other health care services. They also reported taking on average (SD) 1.4 (1.9) medications at the last follow-up visit. In the adjusted model, there was no evidence of a significant improvement in health state ($F(1, 44)=0.13$, $p=0.723$, partial $\eta^2=0.003$, at 8weeks and $F(1, 41)=3.03$, $p=0.089$, partial $\eta^2=0.064$ at 24weeks) (Table 8.12).

Table 8.11 Arm means (SD) in each odd row, medians (IQR) in each even row of health care resources used within the 6-month study period

	Each 1st row: Mean (SD), each 2nd row: Median (IQR)	
	Active intervention (n=25)	Usual care (n=24)
# of currently prescribed medications	1.4 (2.2)	1.5 (1.7)
	0.0 (2.0)	1.0 (2.0)
# of GP visits	1.2 (1.8)	1.5 (1.7)
	1.0 (1.0)	1.0 (2.0)
# of other health care professionals visited	0.6 (0.7)	0.4 (0.5)
	0.0 (1.0)	0.0 (1.0)
# of visits to other health care professional	1.3 (1.8)	0.9 (1.5)
	0.0 (2.0)	0.0 (1.0)
# hospital admissions	0.0 (0.0)	0.0 (0.0)
	0.0 (0.0)	0.0 (0.0)
# of hospital services	1.7 (1.7)	1.7 (1.5)
	1.0 (1.0)	1.0 (1.0)
# of other health services	0.0 (0.0)	0.0 (0.0)
	0.0 (0.0)	0.0 (0.0)

8.6.15 Sensitivity analysis

The results of the multiple imputation trended towards the same direction as those from the complete-case analysis. In general, smaller adjusted group mean differences were observed (**Error! Reference source not found.**).

Table 8.12 Arm means (SD) in each odd row, medians (IQR) in each even row, and differences between arms for EQ-5D health state

	Each 1st row: Mean (SD), each 2nd row: Median (IQR)						Active intervention minus usual care			
	Shape-Up FCT (n=25)			Care as usual (n=24)			Unadjusted Mean Group Difference at 8w (95% CI)	Adjusted Mean Group Difference at 8w (95% CI)	Unadjusted Mean Group Difference at 24w (95% CI)	Adjusted Mean Group Difference at 24w (95% CI)
	Baseline	Change at 8w	Change at 24w	Baseline	Change at 8w	Change at 24w				
EQ-5Q-3L index	1.1 (1.1)	0.0 (1.1)	-0.2 (1.2)	0.7 (1.1)	0.2 (0.6)	0.0 (0.6)	0.2 (-0.4, 0.9)	-	0.2 (-0.4, 0.8)	-
	1.0 (2. 0)	0.0 (0.0)	0.0 (1.0)	0.0 (1.0)	0.0 (1.0)	0.0 (0.0)				
EQ-5D-VAS	69.6 (18.7)	6.2 (15.9)	10.4 (16.2)	79.7 (15.3)	-1.3 (13.3)	-4.8 (16.9)	-2.7 (-12.3, 7.0)	1.4 (-6.6, 9.4)	5.1 (-4.5, 14.8)	7.5 (-1.2, 16.1)
	70.0 (22.0)	3.0 (13.0)	8.0 (20.0)	80.0 (17.0)	-1.0 (19)	-0.5 (12)				

EQ-5D-3L observed range 0-4 within potential range: 0-10. VAS: Visual analogue scale. FCT: following cancer treatment

8.7 Discussion

This is the first study of a health behaviour change intervention demonstrating its feasibility in terms of recruitment, adherence, and retention in endometrial cancer survivors in the UK. The collaboration of the clinical and research team led to an efficient recruitment process. Participants rated the program highly and provided rich feedback for refinement. Furthermore, the estimates from the secondary outcomes can inform the sample size requirements of future trials.

Although it was not possible to recruit the planned sample size, 90% of the expected sample was recruited in less than the projected recruitment period. Delays in the R&D approval of the study were the main reason for having a shorter than planned recruitment period. Thus, future studies should carefully account for those. Having a specific research room to discuss the study with potential participants and the presence of two committed researchers in clinic facilitated a smooth recruitment process. Screening participants using electronic forms and implementing further pre-randomisation eligibility checks from medical notes can minimise randomisation of ineligible participants.

The recruitment rate, while similar between the two sites, was higher compared to the clinician-endorsed mail-out. This might indicate that face-to-face recruitment is a more effective recruitment method for lifestyle interventions trials in this population, but this needs to be balanced with its higher resource requirements.

The overall recruitment estimate was similar or somewhat higher than that in other lifestyle intervention trials, although differences in recruitment strategies, eligibility criteria, cancer site, programme length and intensity do not allow for direct comparisons. For example, the group-based, six-month SUCCEED intervention had a 19% recruitment rate using mail-out (von Gruenigen et al., 2012). A 12-week group-based physical activity intervention

recruited 20% of the eligible endometrial cancer survivors through fliers and telephone recruitment (Rossi et al., 2016). Similar to DEUS, a more intensive lifestyle intervention in UK breast cancer survivors had a mail-out rate of 17% (Scott et al., 2013). The recruitment rate in another feasibility 6-month lifestyle intervention in colorectal cancer survivors was 65% and 24% for in-person and mail-out approaches, respectively (Grimmett et al., 2014). The more convenient telephone-based design might account for the much higher rates compared to the DEUS pilot study. While removing the transport and time barriers would theoretically improve recruitment rates, USA home-based lifestyle interventions recruiting cancer survivors from registries have shown much smaller recruitment rates (5.7%) with women, younger, White survivors and those closer to their cancer diagnosis more likely to enrol (Adams et al., 2014).

Consistent with the literature (Stull et al., 2007) and the qualitative findings, the DEUS pilot study aimed to minimise accrual barriers by enrolling survivors within the "teachable moment" period, capitalising on the endorsement of the study from survivors' clinicians, and having strong behaviour theory-based design. These were also reflected in the reported factors associated with program involvement. Opting for the group-based and face-to-face design aimed to match the preferences indicated in the qualitative study but was in contrast with some previous studies reporting proximity as a particular barrier in this population (Stull et al., 2007). However, most of these studies relied on hypothetical trials, which might differ to real trials.

While decliners in this study tended to initially mention only one reason for non-participation, they generally reported multiple reasons while completing the survey. This allowed for the comprehensive reporting of accrual barriers that could inform future intervention design. Indeed, inconvenience and transport were the main barriers to accrual in the current study. Increasing reach might, therefore, be more feasible with blended

designs of group meetings and remote intervention delivery, especially as the home-based interventions had much lower recruitment rates compared with the face-to-face ones. For the current program, this might mean delivering the first three and last one sessions in person and the remaining four sessions remotely, potentially through web or mobile technology. A pilot weight loss study with endometrial and breast cancer survivors delivered via a mobile application has shown promising results in a pre-post design (McCarroll et al., 2015). However, a recent review examining mobile application for weight management called for further research on this design as it demonstrated lack of evidence-based behaviour change techniques, involvement from health care professionals and poor scientific evaluation (Rivera et al., 2016).

As the perceived benefit from participation was the third most common reason, the results might indicate that the perceived benefit from participation did not outweigh the inconvenience to everyday life. This might be because the study targeted all participants irrespective of their BMI or health behaviours, among whom some believed that they were meeting lifestyle recommendations. Another reason could be the framing of the study as a healthy eating and physical activity intervention (rather than weight loss or following a specific diet), as 13% of decliners were aiming to enrol in commercial weight management programs, such as Weight Watchers. Shifting the framing to weight loss could also be an accrual challenge, as the focus on health promotion was the second most common reason for engaging with this program. A potential adaptation might include an addition of a weight loss section (e.g. stricter portion control) relevant only to those interested in it. Ultimately, it is expected that practising the recommended healthy eating and physical activity behaviours could lead to clinically meaningful weight loss and health promotion in survivors with obesity. In the pilot study, some participants were actively trying to lose

weight and this did not interfere with the group dynamic, indicating the potential for this approach.

The reported barriers differ significantly between the current trial and drug-related cancer trials. In the latter, decliners were mostly concerned about the trial setting, disliked randomisation, and were feeling uneasy with the research process (Mills et al., 2006). In the current study, discomfort with experimentation was reported by 10% of decliners. A potential option to enhance accrual of these survivors is the use of the Zelen design in which participants consent to participate after randomisation. However, this needs to be weighed against the considerably larger sample size required to achieve statistical power in these trials compared to conventional trials (Altman et al., 1995).

Adherence to the intervention as assessed by attendance at sessions was acceptable but not optimal, mainly due to practical reasons. The difficulty of trying to arrange a weekly group meeting with approximately eight people was evident. In an attempt to minimise this, a range of potential times was offered to participants and involved working around the logistics to find the most convenient date for the majority. Given the wide variability of participants' availability, simultaneous offers of a group on a weekday early evening or Saturday morning facilitated engagement in Groups 2 and 3. As this was not possible for group 4, two smaller groups were carried out. In future studies, larger groups will be possible by un-blinding investigators after enough participants are allocated to each trial arm to run two groups (i.e. 32 participants for the current study). This will also be in agreement with preference for a larger group among those who participated in the smaller groups.

The observed adherence was lower compared with the weight loss SUCCEED intervention (84.1%) comprising of 16 group sessions (von Gruenigen et al., 2012) but similar to that of

a group-based 12-week physical activity intervention (Rossi et al., 2016). While this might indicate that survivors are more committed in weight loss programs compared to healthy lifestyle ones, the main reported reasons regarding non-attendance in the current study were around practicalities and life commitments rather than disengagement with the program. Even the adhered participants mentioned convenience reasons as discouraging participation but the peer support as encouraging. Therefore, improving adherence and, simultaneously, retaining the current delivery format is challenging. Even reducing the travel burden with local group sessions may not minimise this type of absences, and, subsequently, improve intervention effectiveness. However, engaged and adhered participants in the current intervention had similar adherence to the SUCCEED study. Sending a standardised e-mail to non-attendees about topics covered in the missed session and preparation for the next session helped maintain their engagement. Furthermore, the lack of dropouts after the second group session indicated the overall acceptability of the intervention.

Indeed, the favourable rating of most program aspects provides confidence that only minor content adaptations are needed. The rich program feedback permits further adaptations of the program to enhance acceptability and engagement such as additions to the physical activity component, removal of the word "cancer" from the title, and redesigning the manual in smaller booklets. The latter was not implemented in this study mainly because of cost constraints, but it could be possible for future studies, as it has already been implemented in a community Shape-Up programme in North Essex, where the original manual has been redesigned in eight booklets. Moreover, some participants mentioned preference for follow-up support. While at the end of each group participants were encouraged to keep in touch with each other and autonomously organise additional group sessions, no communication was evident by the final follow-up. Arranging the independent

first follow-up meeting during the last session might enhance post-intervention communication. The suggested additions for physical activity included more structured exercises in the sessions. This might be particularly beneficial given the lack of observed changes or trends in energy expenditure, and minutes of strength and flexibility exercises. Additionally, structured exercises could improve survivors' self-efficacy, at least temporarily (Hughes et al., 2010), and mirror the available cardiac rehabilitation programs. NICE guidelines recommend structured exercise programmes for sedentary people with various health conditions, but cancer is not yet included (NICE, 2014c).

Regarding the behaviour change techniques (BCTs) evaluated, self-monitoring, SMART goal setting, and social support within the group received high scores as helpful techniques for both dietary and physical activity changes. This was in accordance with the behaviour change literature, which informed the design of the intervention (Michie et al., 2009, French et al., 2011, Cavill and Ells, 2010, NICE, 2014b).

While an evidence-based BCT (French et al., 2011), the self-incentive technique received mixed feedback with some participants struggling to understand the need for self-incentives to encourage behaviour change (as opposed to health incentives) during the program. Furthermore, 14% of participants reported it as the least useful programme aspect. Research in other settings indicates that the coexistence of internal motivation and external motivation is less effective in predicting positive outcomes compared to sole internal motivation (Wrzesniewski et al., 2014) and that rewarding already enjoyable behaviours attenuates intrinsic motivation (Cooke et al., 2011). A judicious and potentially helpful adaptation might then be to use the self-incentives only for promoting non-enjoyable health behaviours.

Interestingly, the section on dealing with external and internal triggers of unhealthy behaviours was ranked both as one of the most useful and one of the least useful aspects. This indicates that a one-size-fits-all approach is highly unlikely to appeal to all program users. Customising the program would require future research to create program entry criteria for allocating participants to a program with or without this topic.

Given the small sample size, the trial was not powered to detect changes in the secondary outcomes. The lack of both power and significance in the secondary outcomes poses difficulties in comparisons with the literature and requires confirmation in larger studies. However, it provided a rich dataset for estimation of outcome measures for an efficacy trial. In this exploratory analysis, the significant improvements in diet, weight, and BMI at 8-weeks indicate the potential effectiveness of the intervention. The mean weight loss was not clinically significant (i.e. within 5-10%) but this was possibly due to the high prevalence of participants with normal weight. Furthermore, it has been argued that clinically significant weight loss might not be necessary for health benefits provided there is sustained practice of health behaviours (Ross, 2016, Dixon and Egger, 2014, Estruch et al., 2016). While not significant, mean differences for various outcomes, such as HRQoL, between the active intervention and control arms generally trended towards the expected direction particularly at 8-week follow-up. However, most of these trends seemed to decline at 24-weeks indicating that a behavioural maintenance program may be required, with potentially similar BCTs to the current one (Teixeira et al., 2015).

Handgrip strength and overall health at 24-weeks showed statistical significant improvements in the active intervention arm in the adjusted model, yet with wide confidence interval. Thus, this result needs to be interpreted with caution given the study power and presence of multiple tests at a=0.05 that increased type I error. Furthermore, relatively high levels of quality of life and functioning were reported which can hinder

future studies with similar samples from observing differences due to ceiling effects. Hence, future studies may implement potential entry cut-offs on quality of life, functioning, and behavioural measures. Limited evidence suggests these ceiling effects might be less common in the FACT-G, which may also have stronger reliability and validity compared with the EORTC-QLQ-C30 (Luckett et al., 2011). Thus, future trials may consider using various instruments to assess HRQoL.

The contamination in the control arm was common but the primary sources were predominantly of informational nature, which might not be an adequate technique for health behaviour change by itself (Michie et al., 2009). This contamination may have arisen from a sample motivated to make behaviour changes. Most previous lifestyle studies have provided the control arm with some lifestyle information ranging from leaflets (von Gruenigen et al., 2012, Hawkes et al., 2013) to counselling sessions (Harrigan et al., 2016). The cases of stronger observed contamination (participation in commercial weight loss programs) could be avoided in future studies by having participants' consent about non-attendance at enrolment.

8.7.1 Strengths

Strengths of the study are a theory-based intervention, standardised delivery of the intervention across groups enhancing its internal validity. Further strengths include reliable and validated outcome measures including objective weight measurements and comprehensive dietary analysis, masked 8-week assessment, and masked participants, researchers, and investigators until intervention allocation. The frameworks for reporting barriers to participation (Kanarek et al., 2012, Mills et al., 2006) provided a comprehensive understanding of these barriers and could be a valuable resource for designing, problem solving and, subsequently, improving accrual in future trials. The CONSORT statement

was also used for reporting the protocol and trial results (**Error! Reference source not found.**). The thoroughly reported BCTs could be incorporated in future meta-regressions to identify ways of influencing various behaviours.

8.7.2 Limitations

Limitations include the self-reported dietary and physical activity data, which contain substantial measurement error owing to social-desirability and recall bias with underreporting of food intake and over-reporting of physical activity, possibly because walking at normal pace was considered as moderate activity (Ferrari et al., 2007, Freedman et al., 2014). Furthermore, the single 24-hour recall does not account for day-to-day variations in dietary intake and, thus, cannot provide objective assessment of individual's intake. Yet, it is less prone to overall bias compared to FFQs making it the recommended and sufficient method for determining difference between two groups in mean usual intake change (NCI, 2016). All recalls were performed during weekdays, adding a day-of-week effect, as population diet is less optimal during weekends (McCarthy, 2014). Some participants had kept a food diary for the day before the assessment to ease the recall process, which may have influenced their dietary intake. The potential differential response bias in dietary reporting between trial arms cannot be excluded and future studies may account for these using sub-sample validation biomarkers (USDA, 2014). The bioelectrical impedance limitations have been discussed in Chapter 5.

Generalisability of the recruited sample is difficult, as it was not possible to collect socio-demographic data from those who declined to participate. The proportions of endometrial cancer histological types match those of larger studies (as shown in studies reviewed in 0). Consistent with similar studies, however, the relatively low median BMI of participants compared to epidemiological studies (Arem et al., 2013b) and high prevalence of meeting

the diet and physical activity guidelines indicate biases due to the healthy volunteer effect. The wide socio-economic and demographic differences of the population pools of the two hospitals (UKDE, 2011) and the similar recruitment rates at both sites provide confidence for the generalisability of the recruitment estimates.

The study was also limited, as participants were not blinded, the final follow-up assessor was not masked, not all BCTs were evaluated, and only two qualitative interviews for evaluation were performed at program completion. In the interviews, participants' responses reflected their written feedback. Hence, the latter was deemed adequate for program evaluation. The lack of reporting for the waist circumference measurement was due to implausible changes observed between time points for some individuals. Finally, the same facilitator delivered all group sessions. As in a pragmatic setting the intervention will be delivered by multiple facilitators, future large-scale studies should also measure differences in intervention delivery between various facilitators.

8.7.3 Conclusion

In conclusion, the low-cost, self-help, group intervention was feasible in terms of recruitment, adherence, and retention. It also showed promising effectiveness. Scaling the intervention will require close monitoring to ensure recruitment targets are met. Scaling could also make it possible for group sessions to be held in local centres, thus, reducing participants' burden. Further qualitative work can inform a blended in-person and remote design to enhance adherence while retaining the valued peer support. A large-scale evaluation of the intervention can inform whether it will be help endometrial cancer survivors improve their health behaviour and, subsequently, improve their well-being and minimise health care costs.

Chapter 9 General Discussion

9.1 Introduction

Having high survival rates, endometrial cancer survivors comprise a high-risk group for obesity-related comorbidities and compromised HRQoL following their cancer diagnosis. Healthy eating and physical activity can improve long-term outcomes but research in this population is limited. Moreover, this population may experience difficulties adopting healthy lifestyle practices but literature is scarce on how to guide intervention development. Personalised behaviour change programmes that are feasible, acceptable, and cost-effective are needed.

Using a range of methodologies, this thesis aimed to develop and pilot a theory-based healthy eating and physical activity program tailored to this population. Study 1 was a systematic review and meta-analysis of obesity and endometrial cancer survival. Study 2 was a systematic review of the literature to explore the association between HRQoL and health behaviours and obesity (Koutoukidis et al., 2015a). Study 3 was an exploratory cross-sectional study piloting the instruments and procedures for the trial and examining various nutrition- and lifestyle-related parameters. Using qualitative methodology, Study 4

explored survivors' attitudes, challenges, and needs towards diet and physical activity (Koutoukidis et al., 2016a). Based on their feedback, an evidence-based behaviour change program was systematically adapted using the intervention mapping framework in study 5. Finally, the intervention was piloted in a randomised controlled trial in study 6. This chapter summarises the research findings and their contribution to the literature together with their limitations and future directions for research and practice. Table 9.1 summarises the results of each study and their contributions to the design and development of the subsequent studies.

9.2 Summary of findings and contribution to the literature

Study 1 updated and confirmed a previous meta-analysis on the inverse association between obesity and overall endometrial cancer survival using a more comprehensive search strategy. It also extended the search on exploring the association between physical activity, diet, and survival and on examining disease-specific and disease-free survival. This extension highlighted the need for studies to examine the relationship between health behaviours and survival and called for better reporting in future studies. Study 2 was the first study to provide strong indications of an association between HRQoL and health behaviours/obesity in endometrial cancer survivors, making the case for using HRQoL as an intermediate endpoint in behavioural intervention trials. Study 3 reinforced the need for behavioural lifestyle interventions targeting this patient population by highlighting their suboptimal health behaviours. Study 4 provided a unique insight into the attitudes, needs, and challenges of UK endometrial cancer survivors about diet and physical activity. It highlighted the treatment side effects and barriers towards healthy lifestyle practices as well as optimal ways for intervention delivery. Thus, both Study 3 and Study 4 crucially informed the adaptation and tailoring of the intervention developed in Study 5. A novel,

tailored, and culturally appropriate lifestyle intervention with high potential for feasibility, effectiveness, and sustainability was the product of study 5. Testing of this intervention in Study 6 confirmed its feasibility and acceptability in the UK setting, and indicated its potential for effectiveness for improving HRQoL in this population. This is an important contribution to this area because this is the first behavioural intervention adapted specifically for endometrial cancer survivors in the UK, and to my knowledge, only the 2nd lifestyle intervention to be developed for this population globally. The following sections provide an overview of each study followed by their limitations and future implications.

Table 9.1 Tabular summary of each study's results and their contribution to the subsequent studies

#	Research Question	Methodology	Results	Conclusions and contribution to the thesis
1.	What is the evidence for an association between health behaviours/obesity with survival in endometrial cancer survivors?	Systematic literature review	• BMI is negatively associated with long-term overall survival. • Cardiovascular disease is the main cause of death in this population. • Low quality evidence suggested BMI is not associated with disease-specific or disease-free survival. • No data existed on dietary exposure and survival. • A negative non-significant trend was observed between physical activity and overall survival in two studies.	• There is no evidence for a beneficial effect of weight loss on survival outcomes. Improvements in diet and physical activity may prevent cardiovascular disease and, subsequently, might improve overall survival. Thus, the adaptation of the intervention in Study 5 shifted the focus from weight loss to improving diet and physical activity (Study 5). • Intermediate outcomes (such as HRQOL) can be of similar importance to survival and may be suitable endpoints for interventions (Study 6).
2.	What is the evidence for an association between health behaviours/obesity with HRQoL in endometrial cancer survivors?	Systematic literature review	• Overall HRQoL and physical well-being were positively associated with meeting lifestyle recommendations, while fatigue was negatively associated with meeting them. • Overall HRQoL and physical well-being were negatively associated with BMI, while fatigue was positively associated with BMI. • Causality could not be inferred due to study design limitations.	• Healthy eating and physical activity are positively associated with various aspects of HRQoL (Study 6). • Behavioural lifestyle interventions to improve suboptimal health behaviours may lead to improvements in HRQoL (Study 6). • There is a need for future research on the health behaviours of this population and how best to develop behaviour change programs (Studies 3 & 4)
3.	What are the health behaviours,	Cross-sectional	• Participants had a high prevalence of overweight and obesity, and moderate diet quality and physical	• The high prevalence of overweight and obesity and suboptimal health behaviours

#	Research Question	Methodology	Results	Conclusions and contribution to the thesis
	nutritional status, and health beliefs of endometrial cancer survivors?	study	activity. • Most participants reported no change in fruit and vegetable intake following their cancer diagnosis. • Sarcopenic obesity was not prevalent in this sample. • Participants reported low risk perception about their health behaviours and low social support towards practising health behaviours. • Regarding types of physical activity interventions, they indicated high preference for walking, of light to moderate intensity, and that they want to start post-treatment.	together with the lack of sarcopenic obesity indicated a need for behavioural lifestyle interventions rather than cachexia-related interventions (Study 5). • The lack of spontaneous changes in fruit and vegetable intake following cancer diagnosis further reinforced the need for behavioural lifestyle interventions (Study 5). • Improving health risk perceptions and social support for practising health behaviours might increase the effectiveness of tailored behaviour change interventions (Study 5). • Intervention developers should consider participants' feedback on preferred physical activity interventions (Study 5). • This study informed the measures for trial evaluation (Study 6).
4.	What are the attitudes, challenges, and needs of endometrial cancer survivors about diet and physical activity?	Qualitative study with focus groups and interviews	• Interpretation of the meaning of healthy lifestyle included every part of well-being. • Benefits to general health but also specific to cancer were reported as reasons for trying to engage in healthy lifestyle behaviours. • Only 50% and 12% of participants reported adhering to the nutrition and physical activity guidelines, respectively.	• Lifestyle interventions in endometrial cancer survivors should be tailored to their treatment-side effects and target barriers of a cognitive, social, and practical nature (Study 5). • Health care professionals should introduce survivors to in-person programs delivered immediately following treatment (Study 5).

#	Research Question	Methodology	Results	Conclusions and contribution to the thesis
			• Treatment effects impeded both diet and physical activity behaviours. The latter were also influenced by social and practical factors. • Insufficient information provision was commonly reported. This was accompanied by a self-directed need to search for such support. • Among the wide preferences for lifestyle interventions delivery, immediately post-treatment and in-person advice were the most favoured timing and method, respectively.	• Adoption of such programs within cancer survivorship care plans should follow feasibility and effectiveness studies demonstrating the potential of such interventions to improve outcomes (Study 6).
5.	Can an existing self-help healthy eating and physical activity intervention program be adapted and tailored to endometrial cancer survivors?	Intervention mapping	• Intervention mapping provided a systematic framework to design a cancer survivor-centred lifestyle intervention. • The systematic approach mapped in detail the program's mechanisms for behaviour change. • Survivors welcomed the intervention and provided essential feedback for its adaptation, such as preference for focusing on behaviours rather than weight.	• The strong involvement of potential service users during the development of the intervention in studies 3-5 provided essential feedback for its adaptation. • The adaptation of an existing evidence-based behaviour change program holds the potential for increased effectiveness, adoption, implementation, and sustainability in the UK cancer care pathway. The program's feasibility, acceptability, and effectiveness should be evaluated through randomised controlled trials (Study 6).
6.	Is it feasible to design an RCT that will assess if the adapted	Randomised controlled trial	• It was feasible to design an RCT comparing Shape-Up following cancer treatment to usual care. • The low-cost, self-help, group intervention was	• Scaling the intervention will require close monitoring to ensure recruitment targets are met.

#	Research Question	Methodology	Results	Conclusions and contribution to the thesis
	programme is more effective than usual care in improving the HRQoL of endometrial cancer survivors?		feasible in terms of recruitment, adherence, and retention. • The intervention also showed promising effectiveness. • Participants in the intervention group rated the program highly and provided essential feedback for refinement, including stronger program focus on physical activity.	• Scaling could also make it possible for group sessions to be held in local centres, thus, reducing participants' burden. • Further qualitative work could inform a blended in-person and remote design to enhance adherence while retaining the valued peer support. • A large-scale evaluation of the intervention could inform whether it will be help endometrial cancer survivors improve their health behaviour and, subsequently, improve their well-being and minimise health care costs.

Parentheses indicate the subsequent studies that each conclusion informed.

9.2.1 What is the evidence of an association between health behaviours/obesity with survival in endometrial cancer survivors?

The research began with a systematic literature review to examine the evidence of an association between health behaviour/obesity and survival outcomes. Study 1 found that BMI was significantly associated with lower overall survival following endometrial cancer treatment. This was primarily the case in the high-quality studies with long-term follow-up. No association was established for disease-free and disease-specific survival, mostly due to high biases and poor reporting in the reviewed studies. It also found suggestive evidence that weight stability after diagnosis and body composition might affect survival. There was limited evidence that physical activity is associated with survival and an absence of evidence for the association between diet and survival.

The study, commenced in 2013, aimed to update the previous literature review that had found mostly studies with high risk of bias that did not allow for a meta-analysis (Arem and Irwin, 2013). A recent meta-analysis on the same topic (Secord et al., 2016) mirrored the current results, yet the methodological differences between them have been discussed in Chapter 4. The association between BMI and overall survival in both meta-analyses supports evidence suggesting that cardiovascular disease is the primary long-term cause of death in endometrial cancer survivors (Ward et al., 2012). The strong links between BMI and unhealthy behaviours with cardiovascular disease in the general literature (Yu et al., 2016) and the prevention of the disease with lifestyle changes (Estruch et al., 2013), when taken together with the above findings, strengthen the need and potential for lifestyle interventions in this population. Exploring survivors' health behaviours, nutritional status, and health beliefs can facilitate the development of such interventions.

9.2.2 What is the evidence of an association between health behaviours/obesity with HRQoL in endometrial cancer survivors?

Study 2 expanded the review from the long-term survival to the short-term HRQoL outcomes, as previous studies had indicated that healthy lifestyle is positively associated with HRQoL (Courneya et al., 2005, Lin et al., 2014, von Gruenigen et al., 2011) in this population but the literature had not been reviewed systematically.

The results indicated that HRQoL and physical well-being were negatively associated with both obesity and not meeting the healthy lifestyle guidelines, particularly physical activity. In contrast, fatigue was positively associated with both obesity and not meeting the guidelines. The magnitude of the effect sizes was similar to those reported in the general population (Ul-Haq et al., 2013) and in survivors of other cancer sites (Blanchard et al., 2008, Schlesinger et al., 2014, George et al., 2014). Moreover, the results also parallel a recent review indicating that obesity is associated with worse surgical outcomes in this population (Orekoya et al., 2016). However, the cross-sectional design of most studies did not allow for causality inference.

The importance of patient reported outcome measures, like HRQoL, has been recently highlighted in the National Cancer Survivorship Initiative Vision (DoH, 2013b). In the presence of funding constraints, HRQoL could be a valuable alternative for evaluating prognosis. The breast cancer literature suggests that HRQoL predicts survival only in advance-stage disease (Montazeri, 2009). Its applicability to endometrial cancer survivors that are mostly diagnosed with early-stage disease remains to be elucidated.

9.2.3 What are the health behaviours, nutritional status, and health beliefs of endometrial cancer survivors?

The exploratory study 3 piloted the instruments for the trial indicating the acceptability of the diet and physical activity measures. However, it also revealed the lack of participants' comprehension for the risk perception and self-efficacy questionnaires. While used mainly in surveys, the results call for their future refinement.

The study also yielded a physically active sample, and confirmed previous surveys that post-treatment, of moderate intensity, walking-based physical activity programs are the most preferable (Karvinen et al., 2006). Yet, participants had moderate diet quality, and high eating behaviour self-efficacy. Many participants were affected by overweight or obesity but not from sarcopenic obesity, similar to breast cancer survivors but unlike ovarian cancer survivors (Balogun et al., 2012). These suggest that health promotion interventions might be more applicable in this population compared to intensive clinical nutritional interventions such as supplementation (Fearon et al., 2013).

Furthermore, participants reported low to average risk perceptions, low social support for health behaviours, and high overall quality of life. Similar to previous studies in cancer survivors (Williams et al., 2013b), the lack of change in the suboptimal fruit and vegetable intake following cancer diagnosis further indicates the need for intervention. An in depth understanding of their attitudes, challenges, and needs regarding diet and physical activity could further inform the design of a lifestyle intervention.

9.2.4 What are the attitudes, challenges, and needs of endometrial cancer survivors about diet and physical activity?

Addressing the last point, the qualitative study 4 suggested that endometrial cancer survivors regard a healthy lifestyle to have a broad meaning with diet and physical activity as core but not sole components. This was consistent with survivors of other cancer sites (Avery et al., 2014). Health promotion was a predominant reason for engaging with healthy lifestyle practices. Social, practical, physiological, and psychological factors also influenced behavioural practice with adherence to lifestyle recommendations suboptimal.

The "teachable moment" of cancer diagnosis was evident only in some participants, because most perceived their lifestyle as healthy, could not tolerate healthy foods or perform specific activities, or were not aware of best practices. The views of endometrial cancer survivors that the window of opportunity for addressing lifestyle issues is at the early post-treatment period reflects views of health care professionals (Coa et al., 2014) and other cancer survivors (Anderson et al., 2013, Karvinen et al., 2006). This short window may vary among individuals given their physical readiness to engage in health-promoting behaviours. As survivors favoured and given the dietary modifications that might be needed during active treatment (Demark-Wahnefried et al., 1997), timing health behaviour interventions towards the end of treatment seems optimal. This also fits with their preferences to engage in physical activity post treatment, as suggested by Study 3. Importantly, their positive attitude towards life after cancer and the belief that cancer established a new landmark in their lives at which they may reappraise their lifestyle may signal an advantageous time to engage them in a healthier lifestyle.

To maximising acceptability, this preferable timing of the intervention can be accompanied with the preferable in-person delivery of interventions tailored to their particular needs.

These novel insights have been capitalised for the design of the intervention. Consistent with the literature (Beeken et al., 2016), survivors did not receive diet or health promotion advice from their health care professionals but would welcome such especially if framed in the context of overall health promotion rather than cancer. Given the lack of lifestyle interventions for this population in the UK, the next attempt was to design such an intervention.

9.2.5 Can an existing self-help healthy eating and physical activity intervention program be adapted and tailored to endometrial cancer survivors?

Study 5 described the successful adaptation of a weight management program for the general population to a healthy eating and physical activity program targeting the population of interest. The intervention was the first to focus on nutrition and physical activity instead of obesity and weight loss in endometrial cancer survivors, a population with high prevalence of overweight, obesity, and related comorbidities. The systematic six-staged process incorporating literature reviews and feedback from service users and relevant stakeholders ensured not only its strong evidence and theoretical basis but also its acceptability to the target population.

The self-help program consists of eight 90-minute group sessions focusing on shaping outcome expectations, knowledge, self-efficacy, and goals about healthy eating and physical activity. The adapted performance objectives included establishment of regular eating, balanced diet, and portion sizes, reduction of sedentary behaviours, increase of lifestyle and organised activities, formulation of a discrepancy-reducing feedback loop for all above behaviours, and trigger management. The main changes included additional information on managing fatigue and bowel issues, together with a weaker and stronger focus on weight

management and resistance exercises, respectively. Social Cognitive Theory and Control Theory guided the matrices' development and selection of behavioural change techniques.

Previous lifestyle interventions in cancer survivors have been guided by Social Cognitive Theory, but the operationalization and reporting of behavioural theory has been limited (Bluethmann et al., 2016, Stacey et al., 2015). In essence, they do not adequately address the questions of why, what, who provided, how, where, when and how much in sufficient detail, as recommended by guidelines for intervention reporting (Hoffmann et al., 2014). The thorough derail of the implemented behavioural change techniques (BCTs) in the current intervention allows for replication and comprehensive evaluation in future meta-analyses. Additionally, the current intervention has plans for adoption and implementation. These aspects are often overlooked at the design stage, yet are key as the value of an effective program that cannot be implemented would be limited. Following the rigorous adaptation process, an evaluation of the intervention was planned.

9.2.6 Is it feasible to design a randomised controlled trial that will assess if the adapted programme is more effective than usual care in improving the HRQoL of endometrial cancer survivors?

Piloting the first health behaviour change intervention in endometrial cancer survivors in the UK, study 6 demonstrated its feasibility, with reasonable recruitment rates, and high retention, but only moderate adherence. Most participants rated the intervention favourably. While most secondary outcomes trended towards the expected direction, the lack of intervention effect for most secondary outcomes is probably due to a lack of power. However, the findings can be used to inform power calculations for a larger study.

The intervention used multiple BCTs. The process evaluation verified the value of behavioural self-monitoring and goal setting for behaviour change (Michie et al., 2009) and

provided insight for reflection on the future use of self-incentives. Participants had varied opinions for the sections about managing external and internal triggers to unhealthy behaviours, with some finding them helpful and some not helpful. However, most participants agreed intervention topics should not be removed. While this highlights that a one-size-fit-all approach is not possible, it might also indicate participants' appreciation for the different needs of each individual on a group intervention. Whether the group format is an efficient intervention remains to be seen with the pilot data underlining the value of social support during the change process, similar to previous studies (Anderson et al., 2010). Few interventions have implemented and reported detailed behavioural evaluations. Informing future trial designs, the results of the current study can be used in combination with those expected from the ASCOT ("Advancing survivorship after cancer diagnosis: outcomes trial") study, a distant, habit-based lifestyle intervention for breast, prostate, and colorectal cancer survivors.

All NICE recommendations about weight management programmes have been followed except the recommendation on the length of the follow-up and the inclusion of a weigh-in at each session (NICE, 2014b), given its feasibility nature and the low focus of the intervention on weight itself, respectively. It also has the potential to impact the NHS Outcome framework domains one ("preventing people from dying prematurely"), two ("enhancing quality of life for people with long term conditions"), and three ("helping people to recover from episodes of ill health or following injury") (DoH, 2014). Additionally, the intervention is in accordance with the National Cancer Survivorship Initiative, envisaging a sustainable personalised lifestyle support for cancer survivors with them playing an active part in the decision-making together with research on patient-reported outcomes (DoH, 2010). Furthermore, it fits within the top ten research priorities that Womb Cancer Alliance produced earlier this year with input from patients, carers, and

clinicians (Wan et al., 2016). Finally, the program fits well under the research priorities for long-term survivorship of the newly established Cancer Nutrition National Institute for Health Research (NIHR) Infrastructure Collaboration (personal communication).

9.3 Limitations

The findings of the present research are subject to limitations. This section presents limitations applicable to most studies. Specific limitations of each study have been detailed in the relevant chapters.

9.3.1 PICOS criteria in systematic reviews

Given the very small number of trials in this population, both reviews aimed to have a broad scope examining a comprehensive list of exposure variables instead of interventions and comparisons with pre-specified cut-offs. While not all PICOS (Population, Intervention, Comparison, Outcome, Study type) have been met and the comparisons were data-driven, the exposure variables were based on the WCRF systematic review on breast cancer survivors (WCRF, 2010). This allowed for a comprehensive review of the literature reported with the PRISMA guidelines (Moher et al., 2009).

9.3.2 Small sample size and non-response bias

All studies in this research involving participants had small sample sizes, which limits the generalisability of the results. This was obvious from the lack of variance in HRQoL questions among others in the exploratory cross-sectional study, which restricted reliable correlational analysis. Hence, it served as a descriptive study.

The 47% response rate in the qualitative study was comparable to that of similar studies but no data existed about non-respondents, signalling potential healthy volunteer bias.

Despite the small sample size of the qualitative study, data saturation was reached, as no new themes were emerging in the final interviews. However, these data may reflect primarily participants well engaged with charities and with high socio-economic status.

Comparable to other interventions, the response rate in the pilot trial was 24%. As with the qualitative study, no socio-demographic data could be collected for the non-respondents. This together with the low baseline BMI compared to epidemiological data indicates the presence of healthy volunteer effect posing challenges to the external validity and generalizability of the study. In contrast, the internal validity of both the assessments and the group sessions was high, for they were performed by the same researcher.

Furthermore, some participants reported that "giving something back" for the care they received and to contribute to future patient care significantly influenced their participation. Thus, recruitment rates might be currently positively skewed compared to those if the program were offered as part of the usual care pathway.

9.3.3 Self-reported data

Both dietary and physical activity data were self-reported and, thus, prone to recall and social-desirability bias. The over-reporting of physical activity was verified using accelerometers. Previous research has indicated that the energy underreporting was 10% using 24-hour recalls (Subar et al., 2003). These measurement errors lead to attenuation of the observed associations with outcomes and to challenges for establishing dose-response relationships. For examining the mean usual intake of a group and its comparison with that of another group, as in the current study, a single 24-hour recall can be sufficient, but further statistical adjustments in future studies accounting for day-to-day variation and post-intervention effects may reduce bias (NCI, 2014b). Using new food-based non-

nutrient dietary indices with similar prediction validity to the current index (Fung et al., 2016) could significantly reduce the burden of dietary analysis.

Recall bias may also be the case in the focus group study where participants were prompted to recall the lifestyle advice received at the end of their treatment, which may have happened as far as five years ago.

9.4 Implications for research and practice

The systematic reviews highlighted the lack of dietary and body composition data. Inclusion of such outcomes and associations with HRQoL and survival in future studies could provide crucial insights for the development of behaviour change interventions. Future prospective studies should focus not only on BMI but also on more reliable measures of body composition accounting for diet and physical activity; its two primary determinants.

The difficulty of analysing the studies included in the systematic reviews together with the widespread presence of high risk of bias call for better quality of reporting in future studies. This will allow for comprehensive meta-analyses and deeper understanding of the relation between nutrition and outcomes. Complying with the currently developed reporting frameworks can aid this process.

On top of the epidemiological evidence, there is a need for mechanistic studies on how diet, physical activity, and body composition may influence endometrial cancer progression and prognosis. Reasonably postulated mechanisms may include improvements in levels of sex-steroid hormones (e.g. oestrogen), insulin and glucose, inflammation, oxidative stress and adipokines (McTiernan, 2008, Betof et al., 2013). These need identification at the pre-clinical and clinical level.

Advances in the field of self-reported dietary data with sophisticated measurement tools, including sensors and cameras, coupled with advances in the field of recovery and predictive dietary biomarkers can decrease the measurement error and increase the validity of the dietary assessment (Stumbo, 2013). Similarly, the use of accelerometers should be combined with self-reported activity for all time points to facilitate objectively measured physical activity. The combination of methods is crucial, since accelerometers do not capture activities such as cycling or weight lifting yet. Clearly, choice of measure needs to be balanced against their cost but it is expected that this will be gradually reduced, as technology develops. From a trial process perspective, electronic instead of paper data collection can reduce cost and minimise data entry errors.

Determining the best methods to facilitate behaviour change in endometrial cancer survivors would require committed and sustained efforts from interdependent actors, including researchers, clinicians, patients, carers, and policymakers. Future interventions trials in cancer survivors should follow the recommendations of the American Society of Clinical Oncology (ASCO) (Ligibel et al., 2015). These include collaboration of multidisciplinary teams, adequate statistical power, and allowance for a sufficient risk of recurrence. In the case of endometrial cancer survivors, the recurrence risk is small making the choice of this outcome challenging. More relevant disease outcomes might include cardiovascular disease prevention and diabetes remission. Two factors that strongly influence the design of future lifestyle intervention trials are cost and selection of primary endpoints. A case study in the recommendations mentions that 10,000 survivors should be recruited for an adequately powered trial on the effect of energy balance questions on disease-free survival in stage I breast cancer.

The huge financial resources for studies with hard endpoints render their funding challenging and the need for strong partnerships between multiple funding bodies and

multidisciplinary research groups. Focusing on the impact of behaviour change on intermediate patient-reported outcomes, such as HRQoL and its domains, can be valuable outcome measures for trials, as they are associated with disease status and the presence of comorbidities. Furthermore, they are in line with the National Cancer Survivorship Initiative (DoH, 2010). The ASCO recommendations also suggest focusing on survivors most in need but also on the largest groups. Yet, these two factors might not necessarily match, as is the case with endometrial cancer survivors.

Health care professionals can play an integral role in the mission of survivorship advancement through lifestyle. Provision of brief lifestyle advice to endometrial cancer survivors at the end of their treatment and directing them to relevant resources, national and local, can help facilitate the lifestyle changes. Given time constraints during clinical appointments, training interventions targeting health care professionals so that they provide very brief advice on the topic and motivate survivors seem feasible and acceptable (Webb et al., 2016b). Combining those interventions with lifestyle interventions targeting survivors may increase intervention efficacy.

Scaling the current intervention will require close monitoring to ensure recruitment targets are met. Scaling could also make it possible for group sessions to be held in local centres, thus, reducing participants' burden. Further qualitative work could inform a blended in-person and remote design to enhance adherence while retaining the valued peer support.

The current intervention has been smoothly delivered in the UCLH Macmillan Cancer Centre without interfering with the centre's busy schedule. General lifestyle programs of informational nature are currently running in both recruitment hospitals. Furthermore, self-help groups for endometrial cancer patients are being established at UCLH. Therefore, the program fits well with the strategic needs assessment in both hospitals. As an initial step, it

could be adopted and implemented in both hospitals to empower lifestyle changes in endometrial cancer survivors. Further feedback from survivors will help intervention refinement, and inform the sustainability of the program as routing part of endometrial cancer care.

Suboptimal health behaviours and obesity are complex societal problems that require substantial investment and engagement not only from clinicians and patients but also from policymakers. Sustained health behaviour change can only be efficacious through multi-level interventions. The current intervention addresses only individual behavioural determinants and should be supported by appropriate policy actions (Lobstein and Brinsden, 2014, WCRF, 2016b) for maximised effectiveness. These concerted efforts could foster the practice of healthy lifestyle behaviours for survivors and their families.

9.5 Concluding remarks

The prevalence of suboptimal health behaviours, comorbidities, and compromised HRQoL in endometrial cancer survivors call for behavioural lifestyle interventions. The proposed self-help group intervention was low-cost and feasible in terms of recruitment, adherence, and retention. A large-scale evaluation of the intervention could inform whether it will help endometrial cancer survivors have a high quality diet and regular physical activity and, subsequently, improve their well-being and minimise health care costs. This will inform the dissemination of the Shape-Up following cancer treatment programme as routine part of the cancer care pathway.

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APPENDICES

Available on the CD-ROM